U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

11986202

SEARCH REQUEST FORM

Requestor's Name: Dwayne C. Jones

Serial Number: 10/087,227

Date: 20 APR 2004 Phone: 2-0578 Art Unit: 1614

mail box REM 4c70 Rm. No. REM 4a71

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

Please search claims 1, 2, 23

in particular the fluoxetine-selective serotonin reuptake inhibitor as the therapeutic agent

and also search the antiglucocorticoid of RU486

and the CNS disorder of major depression

STAFF USE ONLY

Date completed: 4-21-04

Searcher: [illegible]

Terminal time: 77

Elapsed time: prep 30

CPU time:

Total time:

Number of Searches:

Number of Databases:

Search Site

___ STIC

___ CM-1

___ Pre-S

Type of Search

___ N.A. Sequence

___ A.A. Sequence

___ Structure

✓ Bibliographic

Vendors

___ IG

578 STN

___ Dialog

___ APS

___ Geninfo

___ SDC

___ DARC/Questel

___ Other

PTO-1590 (9-90)

STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 119862

TO:	From:
Dwayne C Jones Location: REM/4A71/4C70 Art Unit: 1614 Wednesday, April 21, 2004 Case Serial Number: 10/087227	Barb O'Bryen Location: Biotech-Chem Library Remsen 1A69 Phone: 571-272-2518 BOB barbara.obryen@uspto.gov

Search Notes

RUSH

Dwayne,

For the record, both Medline & Embase consider depression a "mood disorder", not a "CNS disorder". The distinction appears to be disorders that are primarily psychological or have mainly psychological manifestations vs those that involve abnormalities/disease within the anatomical/physical parts of the CNS. (In case you want to pick a nit with the applicants.)

mood disorder

'CNS disorder

Barb

1 of 22
US 2002/065259 A1
9 of 22 WO 96/17192
22 of 22 US 2002/0652594 A1

10 of 22 ~ with oy
22 of 22 WO 95/00478

sira
Search and Information Resources Administration

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Wednesday, April 21, 2004

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT; PLUR=YES; OP=OR	
☐	L15	L14 or l13 or l10 or l9	14
☐	L14	L11 and (mood$6)	12
☐	L13	L11 and (mood near5 disord$4)	6
☐	L12	L11 and (mood near5 disored$4)	0
☐	L11	L8 and CNS	198
☐	L10	L8 and l4	2
☐	L9	L8 and l1	2
☐	L8	L7 and l6	226
☐	L7	fluoxetine or fluval or prozac	2436
☐	L6	RU486 or (Ru near4 486) or mifepristone	1209
☐	L5	RU486 or Ru near4 486 or mifepristone	1209
☐	L4	permeabil$7 near6 (blood near3 brain)	586
☐	L3	(514/651, 1169, 167, 178)[CCLS]	479
☐	L2	(514/651, 1169, 167, 178)![CCLS]	479
☐	L1	(514/651, 1169, 167, 178)[CCLS]	479

END OF SEARCH HISTORY

STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact ***the searcher or contact:***

Mary Hale, Information Branch Supervisor
Remsen Bldg. 01 D86
571-272-2507

Voluntary Results Feedback Form

- *I am an examiner in Workgroup:* [1614] *Example: 1610*
- *Relevant prior art **found**, search results used as follows:*
  - ☐ 102 rejection
  - ☒ 103 rejection
  - ☐ Cited as being of interest.
  - ☒ Helped examiner better understand the invention.
  - ☒ Helped examiner better understand the state of the art in their technology.

  Types of relevant prior art found:
  - ☒ Foreign Patent(s)
  - ☐ Non-Patent Literature
    (journal articles, conference proceedings, new product announcements etc.)
  - ☒ U.S. Patent Pubs
- *Relevant prior art **not found:***
  - ☐ Results verified the lack of relevant prior art (helped determine patentability).
  - ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

Drop off or send completed forms to STIC-Biotech-Chem Library, Remsen Bldg.

```
=> fil medl; d que l10; fil embase; d que l22
FILE 'MEDLINE' ENTERED AT 10:23:17 ON 21 APR 2004

 FILE LAST UPDATED: 20 APR 2004 (20040420/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

L3         12018 SEA FILE=MEDLINE ABB=ON  BLOOD BRAIN BARRIER/CT
L6          3313 SEA FILE=MEDLINE ABB=ON  MIFEPRISTONE/CT
L9           758 SEA FILE=MEDLINE ABB=ON  GLUCOCORTICOIDS+NT/CT(L)AI/CT
L10            3 SEA FILE=MEDLINE ABB=ON  L3 AND (L9 OR L6)


FILE 'EMBASE' ENTERED AT 10:23:17 ON 21 APR 2004
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 FILE COVERS 1974 TO 15 Apr 2004 (20040415/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

L15         4609 SEA FILE=EMBASE ABB=ON  MIFEPRISTONE/CT OR MIFEPRISTONE
                 DERIVATIVE/CT
L18        13421 SEA FILE=EMBASE ABB=ON  BLOOD BRAIN BARRIER/CT
L19         4692 SEA FILE=EMBASE ABB=ON  GLUCOCORTICOID ANTAGONIST+NT/CT
L22           13 SEA FILE=EMBASE ABB=ON  (L15 OR L19) AND L18


=> fil drugu; d que l49; fil wpids; d que l58

FILE 'DRUGU' ENTERED AT 10:23:18 ON 21 APR 2004
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FILE LAST UPDATED: 15 APR 2004       <20040415/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


L39         1952 SEA FILE=DRUGU ABB=ON  BLOOD-BRAIN -BARRIER/CT OR BLOOD-BRAIN-B
                 ARRIER/CT
L40         1457 SEA FILE=DRUGU ABB=ON  MIFEPRISTONE/CT
```

mifepristone / antiglucocorticoids affect on blood-brain barrier

```
L47          753 SEA FILE=DRUGU ABB=ON  GLUCOCORTICOID#(2A)(BLOCK? OR ANTAG? OR
                 INHIBIT?)
L48          162 SEA FILE=DRUGU ABB=ON  ANTIGLUCOCORTICOID#
L49            2 SEA FILE=DRUGU ABB=ON  L39 AND (L40 OR (L47 OR L48))


FILE 'WPIDS' ENTERED AT 10:23:19 ON 21 APR 2004
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FILE LAST UPDATED:          18 APR 2004      <20040418/UP>
MOST RECENT DERWENT UPDATE:     200425        <200425/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE


>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> ADDITIONAL POLYMER INDEXING CODES WILL BE IMPLEMENTED FROM
    DERWENT UPDATE 200403.
    THE TIME RANGE CODE WILL ALSO CHANGE FROM 018 TO 2004.
    SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
    FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
    FIRST VIEW - FILE WPIFV. FREE CONNECT HOUR UNTIL 1 MAY 2004.
    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<


L53           95 SEA FILE=WPIDS ABB=ON  MIFEPRISTON# OR MIFESTON# OR MIFEGYN#
                 OR MIFEPREX OR RU486 OR RU38486 OR RU(W)(486 OR 38486)
L54          228 SEA FILE=WPIDS ABB=ON  GLUCOCORTICOID#(2A)(BLOCK? OR ANTAG? OR
                 INHIBIT?) OR ANTIGLUCOCORTICOID# OR ANTI GLUCOCORTICOID#
L55         1094 SEA FILE=WPIDS ABB=ON  BLOOD BRAIN
L58            2 SEA FILE=WPIDS ABB=ON  (L53 OR L54) AND L55


=> fil uspatf; d que l101; fil capl;d que l85

FILE 'USPATFULL' ENTERED AT 10:23:22 ON 21 APR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 20 Apr 2004 (20040420/PD)
FILE LAST UPDATED: 20 Apr 2004 (20040420/ED)
HIGHEST GRANTED PATENT NUMBER: US6725463
HIGHEST APPLICATION PUBLICATION NUMBER: US2004073984
CA INDEXING IS CURRENT THROUGH 20 Apr 2004 (20040420/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 20 Apr 2004 (20040420/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2004

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
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>>> applications.  USPAT2 contains full text of the latest US          <<<
>>> publications, starting in 2001, for the inventions covered in      <<<
>>> USPATFULL.  A USPATFULL record contains not only the original      <<<
>>> published document but also a list of any subsequent               <<<
>>> publications.  The publication number, patent kind code, and       <<<
>>> publication date for all the US publications for an invention      <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL    <<<
>>> records and may be searched in standard search fields, e.g., /PN,  <<<
>>> /PK, etc.                                                          <<<

>>> USPATFULL and USPAT2 can be accessed and searched together         <<<
>>> through the new cluster USPATALL.  Type FILE USPATALL to           <<<
>>> enter this cluster.                                               <<<
>>>                                                                   <<<
>>> Use USPATALL when searching terms such as patent assignees,       <<<
>>> classifications, or claims, that may potentially change from      <<<
>>> the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L96 (         1)SEA FILE=REGISTRY ABB=ON  RU486/CN
L97 (       367)SEA FILE=USPATFULL ABB=ON  BLOOD-BRAIN BARRIER/CT
L98 (       145)SEA FILE=USPATFULL ABB=ON  L96
L99 (       212)SEA FILE=USPATFULL ABB=ON  (GLUCOCORTICOID#(L)(BLOCK? OR
                ANTAG? OR INHIBIT?) OR ANTIGLUCOCORTICOID# OR ANTI GLUCOCORTICO
                ID#)/IT
L100(       158)SEA FILE=USPATFULL ABB=ON  (GLUCOCORTICOID#(3A)(BLOCK? OR
                ANTAG? OR INHIBIT?) OR ANTIGLUCOCORTICOID# OR ANTI GLUCOCORTICO
                ID#)/AB,TI,CLM
L101            2 SEA FILE=USPATFULL ABB=ON  (L98 OR L99 OR L100) AND L97


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FILE COVERS 1907 - 21 Apr 2004  VOL 140 ISS 17
FILE LAST UPDATED: 20 Apr 2004  (20040420/ED)

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'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L78 (         1)SEA FILE=REGISTRY ABB=ON  RU486/CN
L79 (     11173)SEA FILE=CAPLUS ABB=ON  BLOOD/OBI(A)BRAIN/OBI
L80 (      2925)SEA FILE=CAPLUS ABB=ON  GLUCOCORTICOID#/OBI(L)(BLOCK?/OBI OR
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                ANTAG?/OBI OR INHIBIT?/OBI)
L81 (       242)SEA FILE=CAPLUS ABB=ON  ANTIGLUCOCORTICOID#/OBI
L82 (        19)SEA FILE=CAPLUS ABB=ON  ANTI GLUCOCORTICOID#/OBI
L83 (      1967)SEA FILE=CAPLUS ABB=ON  L78
L84 (    220813)SEA FILE=CAPLUS ABB=ON  BIOLOGICAL TRANSPORT/CT
L85             5 SEA FILE=CAPLUS ABB=ON  L79 AND (L83 OR (L80 OR L81 OR L82))
                AND L84


=> dup rem l10,l49,l85,l22,l58,l101

FILE 'MEDLINE' ENTERED AT 10:23:24 ON 21 APR 2004

FILE 'DRUGU' ENTERED AT 10:23:24 ON 21 APR 2004
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FILE 'USPATFULL' ENTERED AT 10:23:24 ON 21 APR 2004
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PROCESSING COMPLETED FOR L10
PROCESSING COMPLETED FOR L49
PROCESSING COMPLETED FOR L85
PROCESSING COMPLETED FOR L22
PROCESSING COMPLETED FOR L58
PROCESSING COMPLETED FOR L101
L122           22 DUP REM L10 L49 L85 L22 L58 L101 (5 DUPLICATES REMOVED)
                ANSWERS '1-3' FROM FILE MEDLINE
                ANSWERS '4-5' FROM FILE DRUGU
                ANSWERS '6-9' FROM FILE CAPLUS
                ANSWERS '10-21' FROM FILE EMBASE
                ANSWER '22' FROM FILE USPATFULL

=> d ibib ed ab hitrn 1-22

L122 ANSWER 1 OF 22     MEDLINE on STN                  DUPLICATE 3
ACCESSION NUMBER:   1998230272     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 9570346
TITLE:              The genetic variant A of human alpha 1-acid glycoprotein
                    limits the blood to brain transfer of drugs it binds.
AUTHOR:             Jolliet-Riant P; Boukef M F; Duche J C; Simon N; Tillement
                    J P
CORPORATE SOURCE:   Service de Pharmacologie, Faculte de Medecine de
                    Creteil-Paris XII, Creteil, France.. jolliet@univ-
                    paris12.fr
SOURCE:             Life sciences, (1998) 62 (14) PL219-26.
                    Journal code: 0375521. ISSN: 0024-3205.
PUB. COUNTRY:       ENGLAND: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199805
ENTRY DATE:         Entered STN: 19980520
                    Last Updated on STN: 19980520
```

Entered Medline: 19980514
ED Entered STN: 19980520
Last Updated on STN: 19980520
Entered Medline: 19980514
AB The objective of this work was to check the effects of alpha-1 acid glycoprotein (AAG) and of its components, A and F1/S genetic variants, on the brain transfer of drugs they bind in plasma. The relevant extractions of six basic drugs, highly bound to AAG, were measured. We chose three drugs selectively bound to the A variant, disopyramide, imipramine and methadone, one drug mainly bound to the mixture F1/S, mifepristone, and two drugs which were simultaneously bound to the variant A and the mixture F1/S, propranolol and chlorpromazine. Their brain extraction were investigated in rats using the carotid injection technique and the capillary depletion method. Injected drugs were dissolved either in buffer, either in native AAG containing the three variants (A, F1 and S), either in variant A or in variant F1/S solutions. Brain extractions of disopyramide, imipramine and methadone were significantly reduced by native AAG and by variant A. Drug's plasma retention was related to their preferential and almost exclusive binding to A variant, both of them exhibiting the same decrease in brain transfer as compared to a buffered solution. At the opposite, there were no significative differences between the extraction either in buffer, either in AAG or in F1/S solutions, of drugs both bound to A variant and F1/S mixture (chlorpromazine and propranolol) or to the F1/S mixture (mifepristone). In serum, the retentional effect of the A variant on the extraction of disopyramide and imipramine was counteracted by the presence of albumin and lipoproteins, which simultaneously bind these two drugs at a high extent and act as permissive binders. We conclude that AAG binding decreases brain drug transfer when the A variant is mainly and almost exclusively involved in the binding. On the contrary, the entire fraction of the tested drugs when bound exclusively or partly to the mixture F1/S is available for transfer into the brain.

L122 ANSWER 2 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2004077070 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14966384
TITLE: Glucocorticoid-induced apoptosis in CNS microvascular pericytes.
AUTHOR: Katychev Andre; Wang Xueqain; Duffy Alexandra; Dore-Duffy Paula
CORPORATE SOURCE: Multiple Sclerosis Clinical Research Center, Department of Neurology, Division of Neuroimmunology, Wayne State University School of Medicine, Detroit Medical Center, Detroit, Mich. 48201, USA.
CONTRACT NUMBER: NS 143627 (NINDS)
SOURCE: Developmental neuroscience, (2003 Nov-Dec) 25 (6) 436-46. Journal code: 7809375. ISSN: 0378-5866.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040218
Last Updated on STN: 20040415
Entered Medline: 20040414
ED Entered STN: 20040218
Last Updated on STN: 20040415
Entered Medline: 20040414
AB Pericyte loss or migration from its vascular location may be an important step in microvascular remodeling. Decreased pericyte to endothelial ratios are characteristics of newly formed vessels as well as microvessels undergoing regression, and may be due to selective degeneration via necrotic cell death or via programmed cell death. In this study, we have

examined glucocorticoid-induced apoptosis in primary rat CNS pericytes. Characterization of apoptosis was determined using five independent criteria: (1) the translocation of receptors for annexin V from the inner to the outer surface of the plasma membrane, (2) the translocation of cytochrome C from the mitochondria to the cytosol, (3) the induction of DNA fragmentation, (4) the induction of classic changes in cell morphology, and (5) the appearance of TUNEL-positive cells. Incubation of CNS pericytes with dexamethasone induced the appearance of apoptotic cells in a time- and dose-dependent manner. Pericytes express immunologically detectable glucocorticoid receptors, and addition of the glucocorticoid receptor antagonist mifepristone inhibited dexamethasone-induced pericyte apoptosis. That pericytes undergo apoptosis in response to dexamethasone suggests that the regulatory function of this steroid may be important in vascular development and that pericyte apoptotic cell death may accompany vascular regression. Deregulation of pericyte involvement in vascular homeostasis and hemostasis may result in clinical disease.
Copyright 2003 S. Karger AG, Basel

L122 ANSWER 3 OF 22 MEDLINE on STN
ACCESSION NUMBER: 93059897 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1433675
TITLE: Eleventh annual Science Reporters Conference offers cornucopia of medical research stories.
AUTHOR: Skolnick A A; Winker M A
SOURCE: JAMA : journal of the American Medical Association, (1992 Nov 18) 268 (19) 2620-2, 2627-9.
Journal code: 7501160. ISSN: 0098-7484.
PUB. COUNTRY: United States
DOCUMENT TYPE: News Announcement
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19970203
Entered Medline: 19921203
ED Entered STN: 19930122
Last Updated on STN: 19970203
Entered Medline: 19921203

L122 ANSWER 4 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-26108 DRUGU P
TITLE: P-glycoprotein at the blood-brain barrier and analysis of drug transport with positron-emission tomography.
AUTHOR: Hendrikse N H; Bart J; de Vries E G E; Grown H J M; van der Graaf W T A; Vaalburg W
CORPORATE SOURCE: Univ.Groningen
LOCATION: Groningen, Neth.
SOURCE: J.Clin.Pharmacol. (41, Suppl., 48S-54S, 2001) 2 Fig. 4 Tab. 48 Ref.
CODEN: JCPCBR ISSN: 0091-2700
AVAIL. OF DOC.: PET Center, University Hospital, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB P-glycoprotein at the blood-brain barrier (BBB) and analysis of drug transport with positron-emission tomography is reviewed. Drugs discussed include P-glycoprotein substrates: vincristine, vinblastine, vinorelbine, doxorubicin, daunorubicin, idarubicin, epirubicin, etoposide, teniposide, paclitaxel, docetaxel, dactinomycin, mithramycin, mitomycin C, mitoxantrone, amsacrine, trimetrexate, topotecan, zidovudine, ritonavir, indinavir, loperamide, domperidone, ondansnetron, morphine, fentanyl,

verapamil, quinidine, digoxin, ciclosporin, dexamethasone, tacrolimus, progerterone, bilirubin, phenytoin, ivermectin and megestrol acetate. Also discussed are modulators including nifedipine, bepridil, nicardipine, amiodarone, dipyridamole, quinacrine, cinchonine, cefoperazone, ceftriaxone and erythromycin.

L122 ANSWER 5 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1993-16492 DRUGU P E
TITLE: **Glucocorticoids Inhibit** Saturable Insulin Transport into the Central Nervous System in Vivo.
AUTHOR: Baura G D; Foster D M; Porte D Jr; Kahn S E; Schwartz M W
LOCATION: Seattle, Washington, United States
SOURCE: Clin.Res. (41, No. 1, 91A, 1993)
CODEN: CLREAS ISSN: 0009-9279
AVAIL. OF DOC.: University of Washington, Seattle, WA, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Effects of dexamethasone (Dex) on the saturable transport of circulating insulin into the CNS were studied in dogs receiving a euglycemic i.v. insulin infusion. The findings suggested that glucocorticoids (GCs) impair receptor-mediated insulin transport across the blood-brain barrier. Since increasing brain insulin reduces food intake and body adiposity, this observation provides a mechanism to account for the increased body adiposity associated with GC excess. (congress abstract).

L122 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:678486 CAPLUS
DOCUMENT NUMBER: 139:191463
TITLE: **Glucocorticoid blocking** agents for increasing **blood-brain** barrier permeability
INVENTOR(S): Schatzberg, Alan F.; Lindley, Steven; Belanoff, Joseph K.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003162695	A1	20030828	US 2002-87227	20020227

PRIORITY APPLN. INFO.: US 2002-87227 20020227
ED Entered STN: 29 Aug 2003
AB Glucocorticoid blockers, including glucocorticoid receptor antagonists, are effective to prevent glucocorticoid-induced decrease in permeability of the blood-brain barrier and to increase the permeability of the blood-brain barrier. Administration of glucocorticoid blockers, including glucocorticoid receptor antagonists, concomitant with administration of drugs for treating diseases of the central nervous system increases delivery of such drugs into the central nervous system. Corticosterone decreased blood-brain barrier permeability of haloperidol and clozapine in rats.
IT **84371-65-3**, Mifepristone
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as **glucocorticoid** receptor **antagonist**; **glucocorticoid blocking** agents for increasing **blood-brain** barrier permeability of drugs)

L122 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2002:171700 CAPLUS
DOCUMENT NUMBER: 136:210590
TITLE: **Glucocorticoid blocking** agents for increasing **blood-brain** barrier permeability, and use with drugs for treating diseases of the central nervous system
INVENTOR(S): Schatzberg, Alan F.; Belanoff, Joseph K.; Lindley, Steven
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002017930	A2	20020307	WO 2001-US27026	20010829
WO 2002017930	A3	20020516		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001086930	A5	20020313	AU 2001-86930	20010829
US 2002065259	A1	20020530	US 2001-942531	20010829

PRIORITY APPLN. INFO.: US 2000-229278P P 20000830
WO 2001-US27026 W 20010829

ED Entered STN: 08 Mar 2002
AB Glucocorticoid blockers, including glucocorticoid receptor antagonists, are effective to prevent glucocorticoid-induced decrease in permeability of the blood-brain barrier and to increase the permeability of the blood-brain barrier. Administration of glucocorticoid blockers, including glucocorticoid receptor antagonists, concomitant with administration of drugs for treating diseases of the central nervous system increases delivery of such drugs into the central nervous system.
IT **84371-65-3**, Mifepristone
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glucocorticoid blocking** agents for increasing **blood-brain** barrier permeability, and use with drugs for treating diseases of the central nervous system)

L122 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:270008 CAPLUS
TITLE: Methods of treating age-associated memory impairment, mild cognitive impairment, and dementias with cell cycle inhibitors
INVENTOR(S): Reisberg, Barry
PATENT ASSIGNEE(S): New York University, USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004026246	A2	20040401	WO 2003-US29403	20030917

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-411282P P 20020917

ED Entered STN: 02 Apr 2004

AB The invention discloses therapeutic methods for treatment of age-assocd. memory impairment, mild cognitive impairment, Alzheimer's disease, cerebrovascular dementia, and related neurodegenerative conditions by administering an agent capable of inhibiting cell cycle progression, comprising administering one or more agents that are capable of inhibiting neuronal cell cycle progression at either an early cell cycle phase or generally, either alone or in combination with one or more agents capable of reducing mitogenic stimulation.

IT INDEXING IN PROGRESS

L122 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:820780 CAPLUS

DOCUMENT NUMBER: 123:218391

TITLE: Steroids for reducing multidrug resistance to cancer chemotherapeutic agents

INVENTOR(S): Cohn, Suzanne Bourgeois; Gruol, Donald J.

PATENT ASSIGNEE(S): Salk Institute for Biological Studies, USA

SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9517192	A1	19950629	WO 1994-US14624	19941219

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ

RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9514395	A1	19950710	AU 1995-14395	19941219

PRIORITY APPLN. INFO.: US 1993-173243 19931222
WO 1994-US14624 19941219

OTHER SOURCE(S): MARPAT 123:218391

ED Entered STN: 29 Sep 1995

AB Certain steroid-like compds. [I; R1 = H; R2 = OR; or R1R2 = :O; R = H, lower alkyl, Me3Si; R3 = H, Me, or absent if double bond or epoxide bridge joins C9 and C10; R4 = OR', C4-18 cyclic org. group contg. O, N, P, or Si; R' = lower alkyl, Me3Si; R5 = H, OR; or R5C16C17 form a 3-, 5-, 6-, or 7-membered ring; R6 = C(O)CH3, CH(OH)CH3, C(O)CH2OH, (substituted) hydrocarbyl; R9 = H, halo, or absent if double bond or epoxide bridge

joins C9 and C10] are capable of inhibiting the P-glycoprotein-assocd. efflux pump which is considered responsible for multidrug resistance. Chemotherapy can be enhanced by facilitating the accumulation of drug at the target site, with reduced or eliminated competition by the drug efflux system. Thus RU 38486, an antiprogestin, at 5 .mu.M facilitated killing of multidrug-resistant S7CD-5 murine thymoma cells by 20 .mu.M puromycin.

IT **84371-65-3**, RU 38486
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(steroids for reducing multidrug resistance to cancer chemotherapeutic agents)

L122 ANSWER 10 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004069884 EMBASE
TITLE: Hypothalamic-Pituitary-Adrenocortical System and Mood Disorders: Highlights from Mutant Mice.
AUTHOR: Muller M.B.; Uhr M.; Holsboer F.; Keck M.E.
CORPORATE SOURCE: M.B. Muller, Max Planck Institute of Psychiatry, Kraepelinstrasse 2-10, DE-80804 Munich, Germany. muellerm@mpipsykl.mpg.de
SOURCE: Neuroendocrinology, (2004) 79/1 (1-12).
Refs: 109
ISSN: 0028-3835 CODEN: NUNDAJ
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
032 Psychiatry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In recent years, refined molecular technologies and the generation of genetically engineered mice have allowed to specifically target individual genes involved in the regulation of the hypothalamic-pituitary-adrenocortical (HPA) system. Given the fundamental role of the corticotropin-releasing hormone (CRH) system in anxiety, stress-associated pathologies, and mood disorders, we describe genetic modifications of the genes that encode proteins integral to the CRH/CRH receptor system with particular emphasis on conditional gene-targeting strategies. The profile of results, consistent with current knowledge of CRH function from more traditional assays, indicates that enhancement of the CRH function is associated with an activation of the HPA system, an anxious phenotype, alterations in cognitive performance, reductions in food intake, and disturbances of autonomic functions. In general, blockade of CRH activity produces the opposite effects, namely an anxiety-reduced phenotype. Molecular genetic strategies for conditional inactivation or overexpression of the glucocorticoid receptor contribute to our understanding of the genetics of endocrine activity and behavior, the most complex form of biological organization. In addition, we introduce mice with a genetic manipulation in the function of the blood-brain barrier as an animal model for the study of neuroendocrine regulation and, in particular, of HPA system activity. By use of mice deficient for abcb1- (also called multidrug resistance gene 1, mdr1-) type P glycoproteins, it was shown most recently that abcb1-type P glycoproteins control the access of endogenous glucocorticoids into the central nervous system. Thus, the ABCB1-type P glycoprotein function exerts a profound influence on activity and regulation of the HPA system under both basal conditions and during stress. Taken together, these genetically engineered mice are valuable tools for increasing our understanding of HPA system dysregulation in anxiety and stress-related pathologies, including human affective

disorders. The identification and detailed characterization of these molecular pathways will ultimately lead to the development of novel neuropharmacological intervention strategies. Copyright .COPYRGT. 2004 S. Karger AG, Basel.

L122 ANSWER 11 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003453332 EMBASE
TITLE: The Role of Drug Transporters at the Blood-Brain Barrier.
AUTHOR: De Boer A.G.; Van der Sandt I.C.J.; Gaillard P.J.
CORPORATE SOURCE: A.G. De Boer, Division of Pharmacology, Leiden/Amsterdam Ctr. for Drug Res., University of Leiden, Leiden, Netherlands. B.Boer@LACDR.LeidenUniv.nl
SOURCE: Annual Review of Pharmacology and Toxicology, (2003) 43/- (629-656).
Refs: 157
ISSN: 0362-1642 CODEN: ARPTDI
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The blood-brain barrier (BBB) is a dynamic interface between the blood and the brain. It eliminates (toxic) substances from the endothelial compartment and supplies the brain with nutrients and other (endogenous) compounds. It can be considered as an organ protecting the brain and regulating its homomeostasis. Until now, many transport systems have been discovered that play an important role in maintaining BBB integrity and brain homeostasis. In this review, we focus on the role of carrier- and receptor-mediated transport systems (CMT, RMT) at the BBB. These include CMT systems, such as P-glycoprotein, multidrug-resistance proteins 1-7, nucleoside transporters, organic anion transporters, and large amino-acid transporters; RMT systems, such as the transferrin-1 and -2 receptors; and the scavenger receptors SB-AI and SB-BL.

L122 ANSWER 12 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003149468 EMBASE
TITLE: Actions of glucocorticoids and related molecules after traumatic brain injury.
AUTHOR: Rhodes J.K.J.
CORPORATE SOURCE: J.K.J. Rhodes, Intensive Care Unit, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, United Kingdom. jonathanrhodes@blueyonder.co.uk
SOURCE: Current Opinion in Critical Care, (2003) 9/2 (86-91).
Refs: 92
ISSN: 1070-5295 CODEN: COCCF7
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
024 Anesthesiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose of review: Despite 25 years of randomized, controlled trials, the benefit of steroid administration to patients with traumatic brain injury is unproved. Traditionally, glucocorticoids have been used empirically to reduce inflammation and edema. However, it is becoming apparent that the

mechanisms by which steroid molecules might act to improve recovery after traumatic brain injury are numerous. Recent findings: The effects of steroid administration on the central nervous system are not uniform but depend on the population of neurons studied. Definite deleterious effects of steroid administration on neuronal survival have been described. Summary: This review discusses why glucocorticoids might be effective, the considerable laboratory evidence supporting the use of 21-aminosteroids, and the potentially harmful effects of steroid molecules on the brain.

L122 ANSWER 13 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003030996 EMBASE
TITLE: Drug efflux transporters in the CNS.
AUTHOR: Sun H.; Dai H.; Shaik N.; Elmquist W.F.
CORPORATE SOURCE: W.F. Elmquist, Dept. of Pharmaceutical Sciences, Univ. of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, NE 68198, United States. elmqu011@unm.edu
SOURCE: Advanced Drug Delivery Reviews, (21 Jan 2003) 55/1 (83-105).
Refs: 233
ISSN: 0169-409X CODEN: ADDREP
PUBLISHER IDENT.: S 0169-409X(02)00172-2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The central nervous system (CNS) contains important cellular barriers that maintain homeostasis by protecting the brain from circulating toxins and through the elimination of toxic metabolites generated in the brain. The barriers that limit the concentration of toxins and xenobiotics in the interstitial fluids of the CNS are the capillary endothelial cells of the blood-brain barrier (BBB) and the epithelial cells of the blood-cerebrospinal fluid barrier (BCSFB). Both of these barriers have cellular tight junctions and express transport systems which serve to actively transport nutrients into the brain, and actively efflux toxic metabolites and xenobiotics out of the brain. This review will focus on the expression and function of selected drug efflux transporters in these two barriers, specifically the multidrug resistance transporter, p-glycoprotein, and various organic anion transporters, such as multidrug resistance-associated proteins, organic anion transporter polypeptides, and organic anion transporters. These transport systems are increasingly recognized as important determinants of drug distribution to, and elimination from, different compartments of the CNS. Consequences of drug efflux transporters in barriers of the CNS include limiting the distribution of substrates that are beneficial to treat CNS diseases, and increasing the possibility of drug-drug interactions that may lead to untoward toxicities. Therefore, the study of these transporters is important in examining the various determinants of drug delivery to the CNS. .COPYRGT. 2002 Elsevier Science B.V. All rights reserved.

L122 ANSWER 14 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000402819 EMBASE
TITLE: Induction of I.kappa.B.alpha. mRNA expression in the brain by glucocorticoids: A negative feedback mechanism for immune-to-brain signaling.
AUTHOR: Quan N.; He L.; Lai W.; Shen T.; Herkenham M.
CORPORATE SOURCE: Dr. N. Quan, 2214 Postle Hall, Department of Oral Biology, Ohio State University, 305 West 12th Avenue, Columbus, OH 43210, United States. quan.14@osu.edu
SOURCE: Journal of Neuroscience, (1 Sep 2000) 20/17 (6473-6477).

Refs: 27
ISSN: 0270-6474 CODEN: JNRSDS
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Peripheral injection of bacterial endotoxin lipopolysaccharide (LPS) induces brain mRNA expression of the proinflammatory cytokines interleukin-1.beta. (IL-1.beta.) and tumor necrosis factor-.alpha. and the cytokine-responsive immediate-early gene I.kappa.B.alpha.. Peripheral LPS also increases levels of plasma glucocorticoids. Whether the induction of I.kappa.B.alpha. mRNA in the brain after peripheral LPS injection is caused by the feedback action of glucocorticoids has not been determined. In this study, we examined the mRNA expression of I.kappa.B.alpha. and IL-1.beta. in the rat brain by in situ hybridization histochemistry. Injection of the glucocorticoid agonist dexamethasone induced I.kappa.B.alpha. mRNA expression in the brain in a pattern identical to that of LPS injection. LPS but not dexamethasone also induced IL-1.beta. mRNA expression. Pretreatment with dexamethasone 30 min before LPS injection enhanced the expression of I.kappa.B.alpha. mRNA in the brain in a dose-dependent manner. Immobilization of rats for 2 hr (which raises glucocorticoid levels) also induced I.kappa.B.alpha. mRNA expression without inducing the expression of IL-1.beta.. Brain I.kappa.B.alpha. expression induced by peripheral LPS injection was attenuated by pretreatment of rats with the glucocorticoid antagonist RU-486. Finally, increased expression of IL-1.beta. mRNA in the brain was observed at 4 hr after peripheral LPS injection in adrenalectomized rats compared with sham-operated rats. These results reveal that in the brain glucocorticoids selectively induce I.kappa.B.alpha. mRNA expression, which serves as a negative feedback mechanism for peripheral LPS-induced synthesis of proinflammatory cytokines. Such an inhibitory control mechanism may be important for preventing prolonged expression of proinflammatory cytokines in the brain after peripheral immune challenge.

L122 ANSWER 15 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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ACCESSION NUMBER: 2001035298 EMBASE
TITLE: The blood-brain barrier and oncology: New insights into function and modulation.
AUTHOR: Bart J.; Groen H.J.M.; Hendrikse N.H.; Van der Graaf W.T.A.; Vaalburg W.; De Vries E.G.E.
CORPORATE SOURCE: E.G.E. De Vries, Department of Medical Oncology, University Hospital Groningen, P.O. Box 30.001, 9700 RB Groningen, Netherlands. e.g.e.de.vries@int.azg.nl
SOURCE: Cancer Treatment Reviews, (2000) 26/6 (449-462).
Refs: 180
ISSN: 0305-7372 CODEN: CTREDJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The efficacy of chemotherapy for malignant primary or metastatic brain tumours is still poor. This is at least partly due to the presence of the blood-brain barrier (BBB). The functionality of the BBB can be explained by physicochemical features and efflux pump mechanisms. An overview of the literature is presented with emphasis on oncology. The BBB consists of capillary endothelial cells that lack fenestrations and are connected

together with continuous tight junctions, with a high electrical resistance. Permeability of tight junctions can be increased in vitro by contraction of the cytoskeleton, caused by bradykinin agonists. Different efflux pumps are present in the BBB. Examples are P-glycoprotein (P-gp), organic anion transporters, (OAT) and multidrug-resistance-associated proteins (MRP)(1 and 3). These pumps act as a multi-specific efflux pump for various chemotherapeutic drugs. Experiments have shown that P-gp can be inhibited by different non-chemotherapeutic substrates such as cyclosporin A. The functionality in vivo of P-gp can be measured with positron emission tomography and [(11)C]-verapamil or with single photon emission computer tomography and (99m)Tc-sestamibi. MRP(1) and MRP(3) act as organic anion transporters that in vitro act as efflux pumps for substances that are conjugated or co-transported with glutathione and glucuronide, respectively. Methotrexate has been recently demonstrated to be transported by MRP(1) and MRP(3). Results of studies which demonstrate the clinical relevance and applicability of BBB modulators are eagerly awaited. .COPYRGT. 2000 Harcourt Publishers Ltd.

L122 ANSWER 16 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999091539 EMBASE
TITLE: Brain corticosteroid receptor balance in health and disease.
AUTHOR: De Kloet E.R.; Vreugdenhil E.; Oitzl M.S.; Joels M.
CORPORATE SOURCE: Dr. E.R. De Kloet, Division of medical Pharmacology, Leiden/Amsterdam Ctr. for Drug Res., P.O. Box 9503, 2300 RA Leiden, Netherlands. e.kloet@lacdr.LeidenUniv.nl
SOURCE: Endocrine Reviews, (1998) 19/3 (269-301).
Refs: 432
ISSN: 0163-769X CODEN: ERVIDP
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In this review, we have described the function of MR and GR in hippocampal neurons. The balance in actions mediated by the two corticosteroid receptor types in these neurons appears critical for neuronal excitability, stress responsiveness, and behavioral adaptation. Dysregulation of this MR/GR balance brings neurons in a vulnerable state with consequences for regulation of the stress response and enhanced vulnerability to disease in genetically predisposed individuals. The following specific inferences can be made on the basis of the currently available facts. 1. Corticosterone binds with high affinity to MRs predominantly localized in limbic brain (hippocampus) and with a 10-fold lower affinity to GRs that are widely distributed in brain. MRs are close to saturated with low basal concentrations of corticosterone, while high corticosterone concentrations during stress occupy both MRs and GRs. 2. The neuronal effects of corticosterone, mediated by MRs and GRs, are long-lasting, site-specific, and conditional. The action depends on cellular context, which is in part determined by other signals that can activate their own transcription factors interacting with MR and GR. These interactions provide an impressive diversity and complexity to corticosteroid modulation of gene expression. 3. Conditions of predominant MR activation, i.e., at the circadian trough at rest, are associated with the maintenance of excitability so that steady excitatory inputs to the hippocampal CA1 area result in considerable excitatory hippocampal output. By contrast, additional GR activation, e.g., after acute stress, generally depresses the CA1 hippocampal output. A similar effect is seen after adrenalectomy, indicating a U-shaped dose-response dependency of these cellular responses after the exposure to corticosterone. 4. Corticosterone through GR blocks the stress-induced HPA activation in hypothalamic CRH

neurons and modulates the activity of the excitatory and inhibitory neural inputs to these neurons. Limbic (e.g., hippocampal) MRs mediate the effect of corticosterone on the maintenance of basal HPA activity and are of relevance for the sensitivity or threshold of the central stress response system. How this control occurs is not known, but it probably involves a steady excitatory hippocampal output, which regulates a GABAergic inhibitory tone on PVN neurons. Colocalized hippocampal GRs mediate a counteracting (i.e., disinhibitory) influence. Through GRs in ascending aminergic pathways, corticosterone potentiates the effect of stressors and arousal on HPA activation. The functional interaction between these corticosteroid-responsive inputs at the level of the PVN is probably the key to understanding HPA dysregulation associated with stress-related brain disorders. 5. Fine-tuning of HPA regulation occurs through MR- and GR- mediated effects on the processing of information in higher brain structures. Under healthy conditions, hippocampal MRs are involved in processes underlying integration of sensory information, interpretation of environmental information, and execution of appropriate behavioral reactions. Activation of hippocampal GRs facilitates storage of information and promotes elimination of inadequate behavioral responses. These behavioral effects mediated by MR and GR are linked, but how they influence endocrine regulation is not well understood. 6. Dexamethasone preferentially targets the pituitary in the blockade of stress-induced HPA activation. The brain penetration of this synthetic glucocorticoid is hampered by the mdr1a P-glycoprotein in the blood-brain barrier. Administration of moderate amounts of dexamethasone partially depletes the brain of corticosterone, and this has destabilizing consequences for excitability and information processing. 7. The set points of HPA regulation and MR/GR balance are genetically programmed, but can be reset by early life experiences involving mother-infant interaction. 8. Chronically too low or chronically too high levels of corticosteroid hormones during stress and the resultant MR/GR imbalance impair information processing and enhance vulnerability of specific hippocampal neurons. Well documented animal studies show apoptotic cell death and altered neurogenesis after adrenalectomy in dentate gyrus, while hippocampal pyramidal CA3 neurons show atrophy during episodes of chronic stress. Therefore, it is proposed that the maintenance in corticosteroid homeostasis and the balance in MR/GR-mediated effects limit vulnerability to stress-related diseases in genetically predisposed individuals. 9. Corticosteroids control the expression of 'candidate vulnerability genes' in individuals genetically predisposed for stress-related diseases, such as depression.

L122 ANSWER 17 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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ACCESSION NUMBER: 97000346 EMBASE
DOCUMENT NUMBER: 1997000346
TITLE: Exclusion of corticosterone from epithelial mineralocorticoid receptors is insufficient for selectivity of aldosterone action: In vivo binding studies.
AUTHOR: Funder J.; Myles K.
CORPORATE SOURCE: Prof. J. Funder, Baker Medical Research Institute, P.O. Box 348, Prahran, Vic. 3181, Australia
SOURCE: Endocrinology, (1996) 137/12 (5264-5268).
ISSN: 0013-7227 CODEN: ENDOAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Adrenalectomized weanling rats injected with [3H]aldosterone plus excess RU486, with or without a range of doses of nonradioactive aldosterone or corticosterone, show tissue-specific patterns of competition for tracer

binding to mineralocorticoid receptors (MR). From detailed dose-response curves, corticosterone in vivo shows approximately 3% the apparent affinity of aldosterone for MR in colon and kidney, approximately 30% for those in the heart, and approximately 300% in the hippocampus. We interpret these data as evidence that 1) relatively low levels of aldosterone cross the blood-brain barrier; and 2) specificity-conferring mechanisms in addition to the exclusion of corticosterone from epithelial MR are required for selective aldosterone action in sodium homeostasis.

L122 ANSWER 18 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 96035173 EMBASE
DOCUMENT NUMBER: 1996035173
TITLE: Cellular uptake and transport of methylprednisolone at the blood-brain barrier.
AUTHOR: Chen T.C.; Mackic J.B.; McComb J.G.; Giannotta S.L.; Weiss M.H.; Zlokovic B.V.; Young W.; Hodge C.J.
CORPORATE SOURCE: 2025 Zonal Avenue,Los Angeles, CA 90033, United States
SOURCE: Neurosurgery, (1996) 38/2 (348-354).
ISSN: 0148-396X CODEN: NRSRDY
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB METHYLPREDNISOLONE (MP) IS ONE of the most widely used neuroprotective drugs in neurosurgery. Our knowledge of its pharmacokinetics in the brain and, in particular, whether it can penetrate the blood-brain barrier (BBB) and act in the brain parenchyma is still limited. In this study, we used a vascular brain perfusion technique in guinea pigs, combined with a capillary depletion method, to determine brain uptake and transport of MP at the BBB. 3H-Labeled MP was delivered to the brain by carotid arterial infusions lasting from 1 to 10 minutes; the effects of plasma protein binding, different concentrations of MP, and the glucocorticoid receptor inhibitor, RU486, were examined. The existence of a transport system was inferred from the observation that the volume of distribution of MP in the brain after perfusion exceeded by 2.6 to 6.3 times the plasma volume of the cerebrovascular space marker, sucrose. The rates of unidirectional [3H]MP blood-to-brain transport of 0.5 to 0.7 .mu.l per minute per gram indicated significant but slow transfer. MP available for BBB transport was not restricted to its free plasma fraction but, instead, included the albumin- and globulin-bound fractions. A portion of steroid remained concentrated (sequestered) by the capillary endothelium, and from there, the label was distributed into brain parenchyma. Both MP binding and transport at the BBB exhibited saturable kinetics. RU486 produced an inhibition of MP BBB transport and binding with an affinity that seemed to be 30 to 60% higher than that of the steroid itself. We concluded that MP first binds to the brain capillaries and then crosses the BBB at a low rate, most likely by using a saturable mechanism that may involve a cytoplasmic endothelial glucocorticoid receptor.

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on STN
ACCESSION NUMBER: 93330207 EMBASE
DOCUMENT NUMBER: 1993330207
TITLE: Altered luteinizing hormone and prolactin responses to excitatory amino acids during lactation.
AUTHOR: Abbud R.; Smith M.S.
CORPORATE SOURCE: Department of Neurobiology, Univ Pittsburgh School of Medicine, E1440 Biomedical Sciences Tower, 3500 Terrace

Street,Pittsburgh, PA 15261, United States
SOURCE: Neuroendocrinology, (1993) 58/4 (454-464).
ISSN: 0028-3835 CODEN: NUNDAJ
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have used excitatory amino acids as tools to elucidate changes in hypothalamic function associated with lactation, focusing on the regulation of luteinizing hormone (LH) and prolactin secretion. In these studies, we have compared the responsiveness to NMA (N-methyl-D,L-aspartate), an agonist for the N-methy-D-aspartate (NMDA) receptor, with that of kainate, an agonist for another type of glutamate receptor, the kainate receptor. To address the issue of the permeability of the blood-brain barrier to either NMA or kainate, systemic and central administration of the drugs were compared. Four injections of either drug were administered at 10-min intervals to cycling or lactating rats suckling 8 pups. All of these treatment significantly stimulated LH secretion in cycling rats. However, neither systemic injections of NMA (40 mg/kg) or kainate (2.5-3.5 mg/kg), nor third-ventricular administration of NMA (2 .mu.g/2 .mu.l) or kainate (0.2-0.3 .mu.g/2 .mu.l) stimulated LH secretion during lactation. In contrast, LH responses to NMA were observed in lactating animals suckling 2 pups. These data demonstrate that the intensity of the suckling stimulus determines the degree of gonadotropin-releasing hormone (GnRH) neuronal inhibition during lactation. Recovery of the LH response to NMA in animals suckling 8 pups was not observed after treatment with RU 486 to block the effects of progesterone. Thus, the elevated levels of progesterone during lactation do not appear to play a role in inhibiting GnRH neuronal responsiveness. Removal of the 8-pup suckling stimulus for 24 h also did not restore the LH response to NMA. However, treatment with RU 486 and removal of the suckling stimulus for 24 h did restore LH responses to NMA, suggesting that progesterone may play a role in prolonging the recovery of GnRH neuronal responsiveness. The prolactin responses to NMA and kainate changed with the reproductive state of the animal and the site of administration. Central injections of either drug stimulated prolactin release in both cycling and lactating animals. In contrast, whereas systemic administration of NMA stimulated prolactin secretion in cycling animals, kainate had no effect. In the lactating animals, systemic administration of either drug inhibited prolactin secretion. Thus, the difference in the prolactin responses to systemic administration of the drugs may not only be due to a difference in the distribution of kainate and NMDA receptors but also to the steady state level of activity of the prolactin-releasing and -inhibiting factors which is determined by the reproductive state of the animal. In conclusion, lactation alters the responsiveness of several neuronal populations to stimulation by excitatory amino acids. It appears to inhibit GnRH neuronal reponsiveness, as well as to alter the responsiveness of other neurons involved in the regulation of prolactin secretion.

L122 ANSWER 20 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 93088765 EMBASE
DOCUMENT NUMBER: 1993088765
TITLE: Dose-Response relationships of RU 486.
AUTHOR: Heikinheimo O.; Kekkonen R.
CORPORATE SOURCE: Steroid Research Laboratory, Department of Medical Chemistry, University of Helsinki, Siltavuorenpenger 10A,SF-00170 Helsinki, Finland
SOURCE: Annals of Medicine, (1993) 25/1 (71-76).
ISSN: 0785-3890 CODEN: ANMDEU

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Clinical experience has indicated that the effects of RU 486 can be divided into dose-dependent and dose-independent effects. Examples of the dose-dependent effects include the antiglucocorticoid effects of RU 486, whereas pregnancy termination or dilatation of the cervix can be considered dose-independent with the various regimens tested so far. Following oral intake in man, the serum levels of RU 486 are in the micromolar range, and the half-life is approximately 30 hours. The concentrations of RU 486 in myometrial tissue are approximately one-third of those measured in serum. However, due to saturation of alpha 1-acid glycoprotein (AAG), the serum binding protein for RU 486, the serum levels remain similar within the dose range of 100-800 mg of RU 486. The unbound RU 486 is metabolized by two-step demethylation or by hydroxylation. The demethylated and hydroxylated metabolites of RU 486 retain considerable affinities of 9-21% towards the human progesterone receptor, and 45-61% towards the human glucocorticoid receptor (RU 486=100%), suggesting a biological role for the metabolites. Rat serum lacks a specific binding protein for RU 486. Even though the levels of RU 486 in rat adipose tissue are 40 times as high as those seen in serum, the concentrations of RU 486 in rat brain are only 28% of the serum levels. This indicates that diffusion of RU 486 into the central nervous system is restricted by the blood-brain barrier. Hence, the dose-dependency of certain centrally mediated effects of RU 486 might be explained by the limited diffusion of RU 486 into hypothalamic/hypophyseal sites, which seem to be reached only after ingestion of high doses of RU 486. However, the peripheral effects of RU 486, such as termination of pregnancy, are mediated via steroid receptors in target tissues. This suggests that similar biological effects can be attained at considerably lower doses than the ones currently in use.

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ACCESSION NUMBER: 92340803 EMBASE
DOCUMENT NUMBER: 1992340803
TITLE: Eleventh annual science reporters conference offers cornucopia of medical research stories.
AUTHOR: Skolnick A.A.; Winker M.A.
SOURCE: Journal of the American Medical Association, (1992) 268/19 (2620-2622+2627-2629).
ISSN: 0098-7484 CODEN: JAMAAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 004 Microbiology
016 Cancer
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L122 ANSWER 22 OF 22 USPATFULL on STN
ACCESSION NUMBER: 2002:126742 USPATFULL
TITLE: **Glucocorticoid blocking** agents for increasing blood-brain barrier permeability
INVENTOR(S): Schatzberg, Alan F., Los Altos, CA, UNITED STATES
Belanoff, Joseph K., Woodside, CA, UNITED STATES
Lindley, Steven, Redwood City, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002065259	A1	20020530
APPLICATION INFO.:	US 2001-942531	A1	20010829 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-229278P	20000830 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Bret E. Field, Bozicevic, Field and Francis LLP, Suite 200, 200 Middlefield Road, Menlo Park, CA, 94025
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 962
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Glucocorticoid blockers**, including **glucocorticoid** receptor **antagonists**, are effective to prevent glucocorticoid-induced decrease in permeability of the blood-brain barrier and to increase the permeability of the blood-brain barrier. Administration of **glucocorticoid blockers**, including **glucocorticoid** receptor **antagonists**, concomitant with administration of drugs for treating diseases of the central nervous system increases delivery of such drugs into the central nervous system.

IT **84371-65-3**, Mifepristone
(**glucocorticoid blocking** agents for increasing blood-brain barrier permeability, and use with drugs for treating diseases of the central nervous system)

```
=> fil medl; d que l13; d que l14
FILE 'MEDLINE' ENTERED AT 10:25:51 ON 21 APR 2004

 FILE LAST UPDATED: 20 APR 2004 (20040420/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

L4          6553 SEA FILE=MEDLINE ABB=ON  SEROTONIN UPTAKE INHIBITORS/CT
L6          3313 SEA FILE=MEDLINE ABB=ON  MIFEPRISTONE/CT
L8          5924 SEA FILE=MEDLINE ABB=ON  FLUOXETINE# OR PROZAC
L9           758 SEA FILE=MEDLINE ABB=ON  GLUCOCORTICOIDS+NT/CT(L)AI/CT
L13            2 SEA FILE=MEDLINE ABB=ON  L8 AND L4 AND (L9 OR L6)

L1         60884 SEA FILE=MEDLINE ABB=ON  MOOD DISORDERS+NT/CT
L2        659551 SEA FILE=MEDLINE ABB=ON  CENTRAL NERVOUS SYSTEM DISEASES+NT/CT

L4          6553 SEA FILE=MEDLINE ABB=ON  SEROTONIN UPTAKE INHIBITORS/CT
L6          3313 SEA FILE=MEDLINE ABB=ON  MIFEPRISTONE/CT
L9           758 SEA FILE=MEDLINE ABB=ON  GLUCOCORTICOIDS+NT/CT(L)AI/CT
L114           1 SEA FILE=MEDLINE ABB=ON  L4 AND (L9 OR L6) AND (L1 OR L2)

=> s (l13 or l114) not l10

             0 RU486/CN
L123         2 (L13 OR L114) NOT (L10)

=> fil embase; d que l26;d que l34; d que l38

FILE 'EMBASE' ENTERED AT 10:25:53 ON 21 APR 2004
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 FILE COVERS 1974 TO 15 Apr 2004 (20040415/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
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L15         4609 SEA FILE=EMBASE ABB=ON  MIFEPRISTONE/CT OR MIFEPRISTONE
                 DERIVATIVE/CT
L16        94128 SEA FILE=EMBASE ABB=ON  DEPRESSION+NT/CT
L17       608627 SEA FILE=EMBASE ABB=ON  CENTRAL NERVOUS SYSTEM DISEASE+NT/CT
L19         4692 SEA FILE=EMBASE ABB=ON  GLUCOCORTICOID ANTAGONIST+NT/CT
L20        11900 SEA FILE=EMBASE ABB=ON  SEROTONIN UPTAKE INHIBITOR/CT
L21        15659 SEA FILE=EMBASE ABB=ON  FLUOXETINE/CT
L24          709 SEA FILE=EMBASE ABB=ON  (L15 OR L19)(L)(CB OR IT)/CT
L25         3209 SEA FILE=EMBASE ABB=ON  (L20 OR L21)(L)(CB OR IT)/CT
L26            1 SEA FILE=EMBASE ABB=ON  L24 AND L25 AND (L16 OR L17)
```

mifepristone / antiglucocorticoid
+
fluoxetine / SSRI
+
depression
or
CNS disease/disorder

AI = antagonists & inhibitors

previously printed

CB = drug combination
IT = drug interaction

```
L15          4609 SEA FILE=EMBASE ABB=ON  MIFEPRISTONE/CT OR MIFEPRISTONE
                  DERIVATIVE/CT
L19          4692 SEA FILE=EMBASE ABB=ON  GLUCOCORTICOID ANTAGONIST+NT/CT
L20         11900 SEA FILE=EMBASE ABB=ON  SEROTONIN UPTAKE INHIBITOR/CT
L21         15659 SEA FILE=EMBASE ABB=ON  FLUOXETINE/CT
L32          1733 SEA FILE=EMBASE ABB=ON  MAJOR DEPRESSION/CT
L34             2 SEA FILE=EMBASE ABB=ON  (L20 OR L21) AND (L19 OR L15) AND L32


L15          4609 SEA FILE=EMBASE ABB=ON  MIFEPRISTONE/CT OR MIFEPRISTONE
                  DERIVATIVE/CT
L16         94128 SEA FILE=EMBASE ABB=ON  DEPRESSION+NT/CT
L17        608627 SEA FILE=EMBASE ABB=ON  CENTRAL NERVOUS SYSTEM DISEASE+NT/CT
L19          4692 SEA FILE=EMBASE ABB=ON  GLUCOCORTICOID ANTAGONIST+NT/CT
L20         11900 SEA FILE=EMBASE ABB=ON  SEROTONIN UPTAKE INHIBITOR/CT
L21         15659 SEA FILE=EMBASE ABB=ON  FLUOXETINE/CT
L23            30 SEA FILE=EMBASE ABB=ON  (L15 OR L19) AND (L20 OR L21) AND (L16
                  OR L17)
L35          9604 SEA FILE=EMBASE ABB=ON  L20/MAJ OR L21/MAJ
L36          2566 SEA FILE=EMBASE ABB=ON  (L15/MAJ OR L19/MAJ)
L38             5 SEA FILE=EMBASE ABB=ON  L23 AND (L35 OR L36)


=> s (l26 or l34 or l38) not l22

L124            8 (L26 OR L34 OR L38) NOT (L22)  previously printed

=> fil drugu; d que l50

FILE 'DRUGU' ENTERED AT 10:25:54 ON 21 APR 2004
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FILE LAST UPDATED: 15 APR 2004        <20040415/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


L40          1457 SEA FILE=DRUGU ABB=ON  MIFEPRISTONE/CT
L41         14436 SEA FILE=DRUGU ABB=ON  DEPRESSION/CT
L42           874 SEA FILE=DRUGU ABB=ON  (CNS OR CENTRAL NERVOUS SYSTEM)(2A)(DISE
                  ASE# OR DISORDER#)
L43             7 SEA FILE=DRUGU ABB=ON  SEROTONIN-REUPTAKE-INHIBITOR#/CT
L44          1872 SEA FILE=DRUGU ABB=ON  SEROTONIN(W)(UPTAKE OR REUPTAKE)
L45          5976 SEA FILE=DRUGU ABB=ON  FLUOXETIN#/CT
L46          1466 SEA FILE=DRUGU ABB=ON  L44(2A)INHIBITOR#
L47           753 SEA FILE=DRUGU ABB=ON  GLUCOCORTICOID#(2A)(BLOCK? OR ANTAG? OR
                  INHIBIT?)
L48           162 SEA FILE=DRUGU ABB=ON  ANTIGLUCOCORTICOID#
L50             9 SEA FILE=DRUGU ABB=ON  (L40 OR (L47 OR L48)) AND (L46 OR L43
                  OR L45) AND (L41 OR L42)
```

```
=> s l50 not l49

L125            9 L50 NOT L49

=> fil wpids; d que l59

FILE 'WPIDS' ENTERED AT 10:25:58 ON 21 APR 2004
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FILE LAST UPDATED:          18 APR 2004      <20040418/UP>
MOST RECENT DERWENT UPDATE:     200425        <200425/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE


>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> ADDITIONAL POLYMER INDEXING CODES WILL BE IMPLEMENTED FROM
    DERWENT UPDATE 200403.
    THE TIME RANGE CODE WILL ALSO CHANGE FROM 018 TO 2004.
    SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
    FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
    FIRST VIEW - FILE WPIFV. FREE CONNECT HOUR UNTIL 1 MAY 2004.
    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<


L51           362 SEA FILE=WPIDS ABB=ON  FLUOXETIN# OR PROZAC
L52           675 SEA FILE=WPIDS ABB=ON  ((SEROTONIN OR 5HT OR 5(W)(HT OR
                  HYDROXYTRYPTAMINE OR HYDROXY TRYPTAMINE))(1W)(UPTAKE OR
                  REUPTAKE)) (A)INHIBIT?
L53            95 SEA FILE=WPIDS ABB=ON  MIFEPRISTON# OR MIFESTON# OR MIFEGYN#
                  OR MIFEPREX OR RU486 OR RU38486 OR RU(W)(486 OR 38486)
L54           228 SEA FILE=WPIDS ABB=ON  GLUCOCORTICOID#(2A)(BLOCK? OR ANTAG? OR
                  INHIBIT?) OR ANTIGLUCOCORTICOID# OR ANTI GLUCOCORTICOID#
L56         28607 SEA FILE=WPIDS ABB=ON  DEPRESSION
L57          4631 SEA FILE=WPIDS ABB=ON  (CNS OR CENTRAL NERVOUS SYSTEM)(2A)(DISE
                  ASE# OR DISORDER#)
L59             5 SEA FILE=WPIDS ABB=ON  (L53 OR L54) AND (L51 OR L52) AND (L56
                  OR L57)


=> s l59 not l58

L126            4 L59 NOT L58

=> fil uspatf; d que nos 1111; d que nos 1121

FILE 'USPATFULL' ENTERED AT 10:26:03 ON 21 APR 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 20 Apr 2004 (20040420/PD)
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FILE LAST UPDATED: 20 Apr 2004 (20040420/ED)
HIGHEST GRANTED PATENT NUMBER: US6725463
HIGHEST APPLICATION PUBLICATION NUMBER: US2004073984
CA INDEXING IS CURRENT THROUGH 20 Apr 2004 (20040420/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 20 Apr 2004 (20040420/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2004

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together        <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to          <<<
>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from     <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L102(         1)SEA FILE=REGISTRY ABB=ON  RU486/CN
L103(         1)SEA FILE=REGISTRY ABB=ON  FLUOXETINE/CN
L104(       145)SEA FILE=USPATFULL ABB=ON  L102
L105(       212)SEA FILE=USPATFULL ABB=ON  (GLUCOCORTICOID#(L)(BLOCK? OR
                ANTAG? OR INHIBIT?) OR ANTIGLUCOCORTICOID# OR ANTI GLUCOCORTICO
                ID#)/IT
L106(       158)SEA FILE=USPATFULL ABB=ON  (GLUCOCORTICOID#(3A)(BLOCK? OR
                ANTAG? OR INHIBIT?) OR ANTIGLUCOCORTICOID# OR ANTI GLUCOCORTICO
                ID#)/AB,TI,CLM
L107(        36)SEA FILE=USPATFULL ABB=ON  L103(L)((UPTAKE OR REUPTAKE)(W)INHIB
                IT?)/IT
L108(      3960)SEA FILE=USPATFULL ABB=ON  ANTIDEPRESSANTS/CT
L109(      1020)SEA FILE=USPATFULL ABB=ON  DEPRESSION/IT
L110(        28)SEA FILE=USPATFULL ABB=ON  (( FLUOXETIN# OR PROZAC)(5A)((UPTAKE
                 OR REUPTAKE)(W)INHIBIT?))/AB,TI,CLM
L111           1 SEA FILE=USPATFULL ABB=ON  (L104 OR L105 OR L106) AND (L107 OR
                L110) AND (L108 OR L109)



L112(         1)SEA FILE=REGISTRY ABB=ON  RU486/CN
L113(         1)SEA FILE=REGISTRY ABB=ON  FLUOXETINE/CN
L114(       145)SEA FILE=USPATFULL ABB=ON  L112
L115(       212)SEA FILE=USPATFULL ABB=ON  (GLUCOCORTICOID#(L)(BLOCK? OR
                ANTAG? OR INHIBIT?) OR ANTIGLUCOCORTICOID# OR ANTI GLUCOCORTICO
                ID#)/IT
L116(       158)SEA FILE=USPATFULL ABB=ON  (GLUCOCORTICOID#(3A)(BLOCK? OR
                ANTAG? OR INHIBIT?) OR ANTIGLUCOCORTICOID# OR ANTI GLUCOCORTICO
                ID#)/AB,TI,CLM
L117(        36)SEA FILE=USPATFULL ABB=ON  L113(L)((UPTAKE OR REUPTAKE)(W)INHIB
                IT?)/IT
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L118(        28)SEA FILE=USPATFULL ABB=ON  (( FLUOXETIN# OR PROZAC)(5A)((UPTAKE
                OR REUPTAKE)(W)INHIBIT?))/AB,TI,CLM
L119(      2432)SEA FILE=USPATFULL ABB=ON  NERVOUS SYSTEM AGENTS/CT
L120(       702)SEA FILE=USPATFULL ABB=ON  NERVOUS SYSTEM, DISEASE/CT(L)CENTRAL
                /IT
L121          1 SEA FILE=USPATFULL ABB=ON  (L114 OR L115 OR L116) AND (L117 OR
                L118) AND (L119 OR L120)


=> s (l111 or l121) not l101

L127          0 (L111 OR L121) NOT L101

=> fil capl; d que 195; d que 177; d que 168

FILE 'CAPLUS' ENTERED AT 10:26:07 ON 21 APR 2004
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FILE COVERS 1907 - 21 Apr 2004  VOL 140 ISS 17
FILE LAST UPDATED: 20 Apr 2004  (20040420/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L86 (         1)SEA FILE=REGISTRY ABB=ON  RU486/CN
L87 (         1)SEA FILE=REGISTRY ABB=ON  FLUOXETINE/CN
L88 (      2925)SEA FILE=CAPLUS ABB=ON  GLUCOCORTICOID#/OBI(L)(BLOCK?/OBI OR
                ANTAG?/OBI OR INHIBIT?/OBI)
L89 (       242)SEA FILE=CAPLUS ABB=ON  ANTIGLUCOCORTICOID#/OBI
L90 (        19)SEA FILE=CAPLUS ABB=ON  ANTI GLUCOCORTICOID#/OBI
L91 (      3163)SEA FILE=CAPLUS ABB=ON  L87 OR FLUOXETIN#/OBI OR PROZAC/OBI
L92 (      1967)SEA FILE=CAPLUS ABB=ON  L86
L93 (      1603)SEA FILE=CAPLUS ABB=ON  NERVOUS SYSTEM, DISEASE/CT(L)CENTRAL/OB
                I
L94 (      4222)SEA FILE=CAPLUS ABB=ON  NERVOUS SYSTEM AGENTS/CT
L95           1 SEA FILE=CAPLUS ABB=ON  (L93 OR L94) AND (L92 OR (L88 OR L89
                OR L90)) AND L91



L69 (         1)SEA FILE=REGISTRY ABB=ON  RU486/CN
L70 (         1)SEA FILE=REGISTRY ABB=ON  FLUOXETINE/CN
L71 (      2925)SEA FILE=CAPLUS ABB=ON  GLUCOCORTICOID#/OBI(L)(BLOCK?/OBI OR
                ANTAG?/OBI OR INHIBIT?/OBI)
L72 (       242)SEA FILE=CAPLUS ABB=ON  ANTIGLUCOCORTICOID#/OBI
L73 (        19)SEA FILE=CAPLUS ABB=ON  ANTI GLUCOCORTICOID#/OBI
L74 (      3163)SEA FILE=CAPLUS ABB=ON  L70 OR FLUOXETIN#/OBI OR PROZAC/OBI
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L75 (      1967)SEA FILE=CAPLUS ABB=ON  L69
L76 (     21843)SEA FILE=CAPLUS ABB=ON  DEPRESSION/OBI
L77             3 SEA FILE=CAPLUS ABB=ON  L76 AND (L75 OR (L71 OR L72 OR L73))
                  AND L74


L60 (         1)SEA FILE=REGISTRY ABB=ON  RU486/CN
L61 (         1)SEA FILE=REGISTRY ABB=ON  FLUOXETINE/CN
L62 (     11173)SEA FILE=CAPLUS ABB=ON  BLOOD/OBI(A)BRAIN/OBI
L63 (      2925)SEA FILE=CAPLUS ABB=ON  GLUCOCORTICOID#/OBI(L)(BLOCK?/OBI OR
                  ANTAG?/OBI OR INHIBIT?/OBI)
L64 (       242)SEA FILE=CAPLUS ABB=ON  ANTIGLUCOCORTICOID#/OBI
L65 (        19)SEA FILE=CAPLUS ABB=ON  ANTI GLUCOCORTICOID#/OBI
L66 (      3163)SEA FILE=CAPLUS ABB=ON  L61 OR FLUOXETIN#/OBI OR PROZAC/OBI
L67 (      1967)SEA FILE=CAPLUS ABB=ON  L60
L68             1 SEA FILE=CAPLUS ABB=ON  L62 AND (L67 OR (L63 OR L64 OR L65))
                  AND L66


=> s (l95 or l77 or l68) not l85

L128            2 (L95 OR L77 OR L68) NOT (L85) previously printed

=> dup rem l123,l125,l128,l124,l126
FILE 'MEDLINE' ENTERED AT 10:26:50 ON 21 APR 2004

FILE 'DRUGU' ENTERED AT 10:26:50 ON 21 APR 2004
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FILE 'WPIDS' ENTERED AT 10:26:50 ON 21 APR 2004
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PROCESSING COMPLETED FOR L123
PROCESSING COMPLETED FOR L125
PROCESSING COMPLETED FOR L128
PROCESSING COMPLETED FOR L124
PROCESSING COMPLETED FOR L126
L129           22 DUP REM L123 L125 L128 L124 L126 (3 DUPLICATES REMOVED)
                  ANSWERS '1-2' FROM FILE MEDLINE
                  ANSWERS '3-11' FROM FILE DRUGU
                  ANSWERS '12-13' FROM FILE CAPLUS
                  ANSWERS '14-19' FROM FILE EMBASE
                  ANSWERS '20-22' FROM FILE WPIDS

=> d ibib ed ab hitrn 1-22; fil hom

L129 ANSWER 1 OF 22     MEDLINE on STN
ACCESSION NUMBER:    1999078776     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 9861783
TITLE:               Antidepressants inhibit the glucocorticoid stimulation of
                     thyrotropin releasing hormone expression in cultured
                     hypothalamic neurons.
AUTHOR:              Jackson I M; Luo L G
CORPORATE SOURCE:    Division of Endocrinology, Rhode Island Hospital, Brown
                     University School of Medicine, Providence 02903, USA.
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SOURCE: Journal of investigative medicine : official publication of the American Federation for Clinical Research, (1998 Dec) 46 (9) 470-4.
Journal code: 9501229. ISSN: 1081-5589.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990128
Last Updated on STN: 19990128
Entered Medline: 19990113
ED Entered STN: 19990128
Last Updated on STN: 19990128
Entered Medline: 19990113
AB BACKGROUND: The pituitary thyroid axis is frequently effected in human depression possibly due to alteration in hypothalamic thyrotropin releasing hormone (TRH) secretion. Since clinical recovery is associated with normalization of thyroid function, the direct effect of antidepressants on TRH expression in a well established fetal rat hypothalamic neuronal culture system was investigated. METHODS: Fetal rat hypothalamic neurons (day 17) in culture were treated with different concentrations of antidepressants with or without glucocorticoids for 7 days following which TRH content was measured by radioimmunoassay (RIA). RESULTS: The results showed that Imipramine (IMIP), a tricyclic antidepressant (TCA), decreased the TRH content in a dose-dependent manner (from 80.7 +/- 4.9, at 10(-9) mol/L, to 14.1 +/- 0.6, at 10(-5) mol/L, fmol/well; $P < 0.05$). Desipramine (DESI), another tricyclic antidepressant, also decreased the TRH content (from 63.6 +/- 2.5, at 10(-9) mol/L, to 12.6 +/- 0.4, at 10(-5) mol/L, fmol/well; $P < 0.05$). Sertraline (SERT) and **Fluoxetine** (FLUO), serotonin selective reuptake inhibitors (SSRI), also decreased TRH content in a dose dependent manner (from 83.9 +/- 7.9, at 10(-10) mol/L, to 7.6 +/- 0.4, at 10(-5) mol/L, and from 41.66 +/- 2.5, at 10(-8) mol/L, to 17.54 +/- 0.92, at 10(-6) mol/L, fmol/well, respectively; both $P < 0.05$). We then tested the effect of these antidepressants on the Dex stimulation of TRH content. IMIP, DESIP and FLUO at 10(-6) mol/L reduced the TRH response to glucocorticoid stimulation (36.4 +/- 4.0, 56.6 +/- 2.4, 23.75 +/- 4.0, respectively vs 107 +/- 7.5 fmol/well; $P < 0.05$). CONCLUSION: This raises the possibility that the enhanced thyroid function in depression, which we postulate, may result in part from glucocorticoid stimulation of TRH gene expression, can be reversed by antidepressants through a direct effect on the TRH neuron. However, other mechanisms may need to be invoked in addition since basal TRH content was also reduced.

L129 ANSWER 2 OF 22 MEDLINE on STN
ACCESSION NUMBER: 97301664 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9158065
TITLE: RU 486 blocks and **fluoxetine** augments progesterone-induced prolactin secretion in monkeys.
AUTHOR: Pecins-Thompson M; Bethea C L
CORPORATE SOURCE: Division of Reproductive Sciences, Oregon Regional Primate Research Center, Beaverton 97006, USA.
CONTRACT NUMBER: DK9098 (NIDDK)
HD17269 (NICHD)
HD18185 (NICHD)
+
SOURCE: Neuroendocrinology, (1997 May) 65 (5) 335-43.
Journal code: 0035665. ISSN: 0028-3835.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970707
ED Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970707
AB Progesterone (P) stimulates prolactin secretion through an unknown neural mechanism in estrogen (E)-primed female monkeys. Serotonin also stimulates prolactin secretion and this laboratory demonstrated that E induces nuclear progestin receptors (PR) in serotonin neurons. Thus, PR in serotonin neurons could transduce the action of P on prolactin secretion. Studies were performed to determine (1) whether blocking nuclear PR would block P-induced prolactin secretion and conversely; (2) whether increasing serotonin concentrations in the synapse would augment P-induced prolactin secretion. In both studies, female monkeys were spayed, adapted to a vest and tether remote sampling system and catheterized prior to experiments. Monkeys received 2 E-filled silastic implants (3.0 cm) 1-3 weeks prior to study. P (20 mg) in corn oil was injected (s.c.) to transiently increase prolactin secretion. In both studies, each monkey served as its own control. To block nuclear PR and not membrane PR, RU 486 (2 mg/kg, i.m.) or ethanol (control) was administered with the P injection. Relative to the P injection, blood samples were taken twice daily from -30 to +24 h, then every 4 h from +36 to +48 h and once at +65 h. To increase serotonin in the synapse, the serotonin reuptake inhibitor, **fluoxetine** (5 mg/day, i.v.), was infused for 4 weeks. P was injected during the week of vehicle infusion and during the last week of **fluoxetine** infusion. Blood samples were obtained twice daily prior to and following P treatment. Prolactin, E, P and RU 486 concentrations were determined by RIA. RU 486 completely blocked the P-induced prolactin surge (n = 3). In addition, **fluoxetine** significantly increased prolactin secretion during the P-induced prolactin peak compared to equal time points during saline infusion (n = 5). These data indicate that P induces prolactin via a genomic mechanism and not through a membrane action. The data also support a pivotal role for serotonin in the neural regulation of P-induced prolactin secretion.

L129 ANSWER 3 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 2
ACCESSION NUMBER: 2004-07863 DRUGU T P
TITLE: The neuroendocrinology of stress and the pathophysiology and therapy of depression and anxiety.
AUTHOR: Stroehle A
CORPORATE SOURCE: Inst.Max-Planck
LOCATION: Munich, Ger.
SOURCE: Nervenarzt (74, No. 3, 279-92, 2003) 4 Fig. 63 Ref.
CODEN: NERVAF ISSN: 0028-2804
AVAIL. OF DOC.: Klinik fuer Psychiatrie und Psychotherapie, Universitaetsklinikum Charite, Humboldt-Universitaet zu Berlin, Schumannstr. 20/21, 10117 Berlin, Germany. (e-mail: andreas.stroehle@charite.de).
LANGUAGE: German
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The neurophysiology of stress is reviewed with reference to the psychopharmacology of depression, panic disorders and post-traumatic stress disorders. Mechanisms of action of drugs including antidepressives and neuroactive steroids, and possible new methods of treatment of stress disorders are discussed in relation to the results of animal experiments and recent clinical studies.

L129 ANSWER 4 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 3

ACCESSION NUMBER: 2003-44619 DRUGU P E
TITLE: Neurosteroids in depression: a review.
AUTHOR: van Broekhoven F; Verkes R J
CORPORATE SOURCE: Univ.Nijmegen
LOCATION: Nijmegen, Neth.
SOURCE: Psychopharmacology(Berlin) (165, No. 2, 97-110, 2003) 1 Fig. 1 Tab. 211 Ref.
CODEN: PSCHDL ISSN: 0033-3158
AVAIL. OF DOC.: Dep. of Psychiatry, Unit for Clinical Psychopharmacology and Neuropsychiatry, Univ. Medical Center Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands. (e-mail: f.vanbroekhoven@czzopsy.azn.nl).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The use of neurosteroids in depression is reviewed. The synthesis of neurosteroids is described. The therapeutic effects of neurosteroids (e.g., allopregnanolone (ALL), pregnanolone, 3alpha,5alpha-tetrahydrodeoxycorticosterone (3alpha,5alpha-TH DOC), dehydroepiandrosterone (DHEA), benzodiazepines (e.g., chlordiazepoxide), and SSRI (fluoxetine, paroxetine, sertraline)) are discussed. This review suggests that indirect genomic and non-genomic mechanisms are involved in the neurosteroidogenic pathophysiology of depression.

L129 ANSWER 5 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2004-13098 DRUGU P E
TITLE: Stress responsive neurohormones in depression and anxiety.
AUTHOR: Stroehle A; Holsboer F
CORPORATE SOURCE: Univ.Berlin; Max-Planck-Inst.Psychiat.Munich
LOCATION: Berlin; Munich, Ger.
SOURCE: Pharmacopsychiatry (36, Suppl. 3, S207-S214, 2003) 2 Fig. 63 Ref.
CODEN: PHRMEZ ISSN: 0176-3679
AVAIL. OF DOC.: Department of Psychiatry and Psychotherapy, Charite - University Medicine Berlin, Campus Charite-Mitte (CCM), Schumannstr. 20/21, 10117 Berlin, Germany. (e-mail: andreas.stroehle@charite.de).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The role of stress response hormones (the hypothalamic pituitary adrenocortical (HPS) system) in depression and anxiety (panic disorder, post-traumatic stress disorder) is reviewed. Modulation of the stress response by CRH, corticosteroids their receptors, and the role of natriuretic peptides and neuroactive steroids are reviewed. Antidepressants have been shown to decrease baseline and stress induced levels of plasma ACTH and corticosterone in rats. Fluoxetine may modulate the concentrations of those neuroactive steroids that act primarily at ion receptors, thereby inducing behavioral changes. CRH-R1 and **glucocorticoid** receptor **antagonists** and ANP receptor agonists may provide future treatment options more closely related to the pathophysiology of the disorders. (conference paper: 1st International Charite Conference on Psychiatric Research, Berlin, Germany, October, 2002). (No EX).

L129 ANSWER 6 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-24833 DRUGU T
TITLE: Antagonists of substance P as a new class of antidepressives.
AUTHOR: Lieb K; Herpfer I; Fiebich B L; Berger M
CORPORATE SOURCE: Univ.Freiburg
LOCATION: Freiburg, Ger.

SOURCE: Dtsch.Med.Wochenschr. (127, No. 48, 2563-65, 2002) 1 Fig. 2 Tab. 10 Ref.
CODEN: DMWOAX ISSN: 0012-0472
AVAIL. OF DOC.: Universitaetsklinikum Freiburg, Abteilung fuer Psychiatrie und Psychotherapie, Hauptstrasse 5, 79104 Freiburg, Germany. (e-mail: klaus_lieb@psyallg.ukl.uni-freiburg.de).
LANGUAGE: German
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The therapeutic use of antagonists of substance P receptors as antidepressives is reviewed with reference to the working principle of this therapeutic approach, the role of substance P-containing neurons in the genesis of stress, and the effects of substance P antagonists in animal models of depression and clinical studies. The various classes of other antidepressive drugs are also mentioned.

L129 ANSWER 7 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-25042 DRUGU T
TITLE: Expanding the horizons of depression: beyond the monoamine hypothesis.
AUTHOR: Hindmarch
LOCATION: Guildford, U.K.
SOURCE: Hum.Psychopharmacol. (16, No. 3, 203-18, 2001) 1713 Ref.
CODEN: HUPSEC ISSN: 0885-6222
AVAIL. OF DOC.: HPRU Medical Research Centre, University of Surrey, Egerton Road, Guildford, Surrey, GU2 5XP, England. (e-mail: i.hindmarch@surrey.ac.uk).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Depression is reviewed with reference to the monoamine hypothesis, the hypothalamic pituitary adrenal (HPA) axis, substance P, hypothalamic pituitary thyroid (HPT) axis, hippocampal formation in depression, second messenger pathways, N-methyl-D-aspartate (NMDA) receptors, abnormal calcium homeostasis, cytokines and the link between stress and depression, and monitoring the efficacy of antidepressant action. Drugs mentioned include imipramine, iproniazid, tianeptine, citalopram, fluoxetine, mirtazepine, mianserin, reboxetine, buproprion, aminoglutethimide, metyrapone, ketoconazole, cortisol, dexamethasone and MK-869. There are many possibilities for development of novel antidepressants in the future. Further research is required to clarify the roles of the various systems involved.

L129 ANSWER 8 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-16190 DRUGU T
TITLE: On the feasibility of designing new antidepressants.
AUTHOR: Pinder R M
LOCATION: West Orange, N.J., USA
SOURCE: Hum.Psychopharmacol. (16, No. 1, 53-59, 2001) 2 Tab. 33 Ref.
CODEN: HUPSEC ISSN: 0885-6222
AVAIL. OF DOC.: International Medical Director CNS and Cardiovascular, Organon Inc., 375 Mt. Pleasant Avenue, West Orange, NJ 07052, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The feasibility of designing new antidepressants is reviewed. Antidepressants (tricyclic antidepressants (TA), 5-HT noradrenaline reuptake inhibitors (SNRI), MAOI, SSRI, noradrenaline and 5-HT specific antidepressants (NASSA), noradrenaline receptor inhibitors (NRI) and

atypical antidepressants) widely available in Europe are presented. Designing new antidepressants, and old and new drug discovery are discussed. A new pharmacology for third generation antidepressants is described. While new antidepressant moieties will undoubtedly emerge, optimal use of the new research tools will necessitate a more sophisticated level of knowledge about the true causes of depression.

L129 ANSWER 9 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-01969 DRUGU T E
TITLE: The corticosteroid receptor hypothesis of depression.
AUTHOR: Holsboer F
CORPORATE SOURCE: Max-Planck-Inst.Psychiatry
LOCATION: Munich, Ger.
SOURCE: Neuropsychopharmacology (23, No. 5, 477-501, 2000) 3 Fig. 208 Ref.
CODEN: NEROEW ISSN: 0893-133X
AVAIL. OF DOC.: Max Planck Institute of Psychiatry, Kraepelinstr. 2-10, D-80804 Munich, Germany.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Clinical and preclinical data on the corticosteroid receptor hypothesis of depression are reviewed. Mouse genetics and molecular pharmacology are the most promising research fields suited for identifying genes predisposing to depression. Impaired central stress hormone regulation is causally involved in the development and course of depression. Experimental evidence is provided, suggesting that the mechanism of action of antidepressants includes normalization of hypothalamic-pituitary-adrenocortical (HPA) activity. While clinical studies are needed to test whether specific intervention at various levels of stress hormone regulation are equal or superior to current antidepressants (MAOI, SSRI, norepinephrine reuptake **inhibitors**, **serotonin reuptake** enhancer), basic studies need to elaborate intracellular signaling and DNA effects of antidepressants and how stress hormones interfere.

L129 ANSWER 10 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-00189 DRUGU T
TITLE: Future therapeutic targets in mood disorders: the glucocorticoid receptor.
AUTHOR: McQuade R; Young A H
CORPORATE SOURCE: Univ.Newcastle
LOCATION: Newcastle upon Tyne, U.K.
SOURCE: Br.J.Psychiatry (177, Nov., 390-95, 2000) 1 Fig. 1 Tab. 51 Ref.
CODEN: BJPYAJ ISSN: 0007-1250
AVAIL. OF DOC.: The Stanley European Bipolar Research Centre, Psychiatry Research Laboratory, The Medical School, Framlington Place, newcastle upon Tyne NE2 4H, England. (A.H.Y.). (e-mail: a.h.young@ncl.ac.uk).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The future therapeutic targets in mood disorders with reference to the glucocorticoid receptor (GR) are reviewed. The hypothalamic-pituitary-adrenal (HPA) axis regulation, dysfunction and psychiatric disorders are described. Antidepressants, mood stabilizers and brain GR are discussed. The effects of desipramine, amitriptyline, imipramine, maprotiline, fluoxetine, citalopram, lithium and electroconvulsive shock on type II GR in various experimental systems are presented. The primary consequences of hypercortisolemia and the future therapeutic targets

(dehydroepiandrosterone (DHEA, prasterone), ketoconazole, metyrapone, aminogluthemide, dexamethasone and RU-486 (mifepristone)) are explained. Drugs designed specifically to up-regulate GR may be integral to future strategies in treating mood disorders.

L129 ANSWER 11 OF 22 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1993-31040 DRUGU T S
TITLE: Clinical Management of the Depressed Geriatric Patient: Current Therapeutic Options.
AUTHOR: Mendels J
LOCATION: Philadelphia, Pennsylvania, United States
SOURCE: Am.J.Med. (94, No. 5A, 13S-18S, 1993) 3 Fig. 3 Tab. 26 Ref.
CODEN: AJMEAZ ISSN: 0002-9343
AVAIL. OF DOC.: Philadelphia Medical Institute, 1015 Chestnut Street, Philadelphia, Pennsylvania 19096, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Current therapeutic drug options for the depressed geriatric patient are reviewed with special reference to the clinical efficacies and adverse reaction liabilities of tricyclic antidepressants (TCA), MAOI and selective 5-HT reuptake inhibitors (SSRI). Although all these drug classes are effective antidepressants, SSRI appear to be safer and to have a wider therapeutic index than either TCA or MAOI. Among SSRI, sertraline (SE) is particularly well suited to treating the elderly depressive. Atypical antidepressants appear to be poorly suited to this end. Nonpharmacological management options include psychotherapy and ECT. Drugs which can precipitate depression in the elderly are also mentioned. (congress).

L129 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:100942 CAPLUS
DOCUMENT NUMBER: 140:139528
TITLE: Combination therapy for **depression**, prevention of suicide, and various medical and psychiatric conditions
INVENTOR(S): Migaly, Peter
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004010932	A2	20040205	WO 2003-US23326	20030725

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-319436P P 20020730
ED Entered STN: 08 Feb 2004
AB The present invention relates to a new method of treatment for persons

meeting diagnoses for major depressive disorder, or other unipolar (non-bipolar, nonpsychotic and non-treatment resistant) depression. The method comprises administering a combination of two categories of drugs, antipsychotics or dopamine system stabilizers, in combination with a newer antidepressant such as a selective serotonin reuptake inhibitor, as initial treatment or as soon as possible. The method targets the prevention of suicide, and provides other benefits including preventing disease progression development of tolerance toward the antidepressants. Another aspect of the invention relates to using the method for alleviating cognitive distortion and related functional impairment or health risks, and/or using the method for smoking cessation or nicotine withdrawal.

IT **54910-89-3, Fluoxetine**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy for **depression**, prevention of suicide, and various medical and psychiatric conditions)

L129 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:653114 CAPLUS
DOCUMENT NUMBER: 140:139203
TITLE: Altered Glucocorticoid Rhythm Attenuates the Ability of a Chronic SSRI to Elevate Forebrain 5-HT: Implications for the Treatment of **Depression**
AUTHOR(S): Gartside, S. E.; Leitch, M. M.; Young, A. H.
CORPORATE SOURCE: The Medical School, School of Neurology, Neurobiology and Psychiatry, Psychobiology Research Group, University of Newcastle upon Tyne, Newcastle, UK
SOURCE: Neuropsychopharmacology (2003), 28(9), 1572-1578
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 22 Aug 2003
AB Both glucocorticoids and selective serotonin reuptake inhibitors (SSRIs) alter aspects of 5-HT function including somatodendritic 5-HT1A autoreceptor sensitivity. Many depressed patients prescribed SSRIs have pre-existing flattened diurnal gluococorticoid rhythm. In these patients, interactions between flattened glucocorticoid rhythm and chronic SSRIs, which impact on the SSRI's ability to elevate forebrain 5-HT, may alter clin. efficacy. To address this issue rats underwent implantation of slow-release corticosterone (75 mg pellet s.c.) (to flatten the glucocorticoid rhythm) or sham surgery, and injection of fluoxetine (10 mg/kg/day i.p., 12 days) or vehicle. Using microdialysis in the frontal cortex we found that (21 h after the last injection) extracellular 5-HT was elevated in fluoxetine- or corticosterone-treated animals, but not in those treated with corticosterone plus fluoxetine. In fluoxetine-treated animals, blockade of terminal reuptake by local perfusion of fluoxetine increased 5-HT to the same level as it did in controls, suggesting normal terminal 5-HT release after chronic fluoxetine. However, 5-HT levels following local reuptake blockade in both the corticosterone and corticosterone plus fluoxetine groups were lower than controls, suggesting a corticosterone-induced decrease in terminal release. Finally in fluoxetine, corticosterone, and corticosterone plus fluoxetine groups, there was marked 5-HT1A receptor desensitization, evidenced by attenuation of the decrease in 5-HT release following systemic fluoxetine injection. The data indicate that, despite desensitization of 5-HT1A autoreceptors, concurrent flattened glucocorticoid rhythm compromises the ability of SSRIs to elevate forebrain 5-HT. These findings suggest a potential mechanism for the reduced antidepressant efficacy of SSRIs in those patients with pre-existing glucocorticoid abnormalities.

IT **54910-89-3, Fluoxetine**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(altered glucocorticoid rhythm attenuates chronic SSRI elevation of forebrain 5-HT)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L129 ANSWER 14 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003475954 EMBASE
TITLE: Pharmacological treatments for heroin and cocaine addiction.
AUTHOR: Van Den Brink W.; Van Ree J.M.
CORPORATE SOURCE: W. Van Den Brink, Dept. of Pharmacology and Anatomy, Rudolf Magnus Inst. of Neuroscience, Utrecht University, Utrecht, Netherlands. w.vandenbrink@amc.uva.nl
SOURCE: European Neuropsychopharmacology, (2003) 13/6 (476-487). Refs: 137
ISSN: 0924-977X CODEN: EURNE8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 032 Psychiatry
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Aims: To provide an overview of the pharmacological options for the treatment of heroin- and cocaine-dependent patients based on known biochemical pathways to addiction and the chronic disease model as a starting point for treatment planning. Results: Recent pre-clinical and clinical studies indicate that different brain structures and different neurotransmitters are involved in different stages of the addiction process. In addition, clinical experience shows that heroin and cocaine addiction can best be conceptualised and treated as a chronic, relapsing disorder with the following treatment goals: crisis intervention, cure or recovery (detoxification, relapse prevention) and care or partial remission (stabilization and harm reduction). The various high-quality studies, systematic literature reviews and formal meta-analyses clearly demonstrate that today many proven effective interventions are available for crisis intervention, detoxification, stabilization and harm reduction for heroin-dependent patients. Interventions directed at relapse prevention are still problematic and only effective in a minority of motivated patients in stable living conditions and adequate social support. In contrast, no proven effective pharmacological interventions are available for the treatment of cocaine-dependent patients, maybe with the exception of some patient groups that seem to benefit from treatment with disulfiram or amantadine. Treatment innovations are primarily based on experimental animal studies. Newly developed cannabinoid receptor antagonists and cortisol synthesis inhibitors show great promise. Conclusion: Heroin addiction is a chronic relapsing disease that is difficult to cure, but stabilization and harm reduction can greatly increase the life time expectancy and the quality of life of the patient, his direct environment and society as a whole. Currently, no proven effective pharmacological interventions are available for cocaine addiction, and treatment has to rely on existing cognitive behaviour therapies combined with contingency management strategies. .COPYRGT. 2003 Elsevier B.V./ECNP. All rights reserved.

L129 ANSWER 15 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004031336 EMBASE
TITLE: Stress Responsive Neurohormones in Depression and Anxiety.

AUTHOR: Strohle A.; Holsboer F.
CORPORATE SOURCE: Dr. A. Strohle, Dept. of Psychiat. and Psychotherapy, Char. - Univ. Medicine Berlin, Campus Charite-Mitte (CCM), Schumannstr. 20/21, 10117 Berlin, Germany. andreas.stroehle@charite.de
SOURCE: Pharmacopsychiatry, (2003) 36/SUPPL. 3 (S207-S214). Refs: 63
ISSN: 0176-3679 CODEN: PHRMEZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Clinical and preclinical studies have gathered substantial evidence that stress response alterations play a major role in the development of major depression, panic disorder and posttraumatic stress disorder. The stress response, the hypothalamic pituitary adrenocortical (HPA) system and its modulation by CRH, corticosteroids and their receptors as well as the role of natriuretic peptides and neuroactive steroids are described. Examplarily, we review the role of the HPA system in major depression, panic disorder and posttraumatic stress disorder as well as its possible relevance for treatment. Impaired glucocorticoid receptor function in major depression is associated with an excessive release of neurohormones, like CRH to which a number of signs and symptoms characteristic of depression can be ascribed. In panic disorder, a role of central CRH in panic attacks has been suggested. Atrial natriuretic peptide (ANP) is causally involved in sodium lactate-induced panic attacks. Furthermore, preclinical and clinical data on its anxiolytic activity suggest that non-peptidergic ANP receptor ligands may be of potential use in the treatment of anxiety disorders. Recent data further suggest a role of 3.alpha.-reduced neuroactive steroids in major depression, panic attacks and panic disorder. Posttraumatic stress disorder is characterized by a peripheral hyporesponsive HPA-system and elevated CRH concentrations in CSF. This dissociation is probably related to an increased risk for this disorder. Antidepressants are effective both in depression and anxiety disorders and have major effects on the HPA-system, especially on glucocorticoid and mineralocorticoid receptors. Normalization of HPA-system abnormalities is a strong predictor of the clinical course, at least in major depression and panic disorder. CRH-R1 or glucorticoid receptor antagonists and ANP receptor agonists are currently being studied and may provide future treatment options more closely related to the pathophysiology of the disorders.

L129 ANSWER 16 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999436097 EMBASE
TITLE: [What has 1999 brought us? New drugs, variations and side effects].
WAT HEEFT 1999 ON GEBRACHT? NIEUWE GENEESMIDDELEN, VARIATIES EN BIJWERKINGEN.
SOURCE: Geneesmiddelenbulletin, (2000) 34/1 (6-10).
ISSN: 0304-4629 CODEN: GNMBAI
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Dutch

L129 ANSWER 17 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 1998227686 EMBASE
TITLE: Psychoneuroendocrinology of depression: Hypothalamic-pituitary-gonadal axis.
AUTHOR: Young E.; Korszun A.
CORPORATE SOURCE: Dr. E. Young, Department of Psychiatry, University of Michigan, Mental Health Research Institute, 205, Zina Pitcher Place, Ann Arbor, MI 48109-1720, United States
SOURCE: Psychiatric Clinics of North America, (1998) 21/2 (309-323).
Refs: 92
ISSN: 0193-953X CODEN: PCAMDG
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
032 Psychiatry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Women are more susceptible than men to depression, particularly during periods of rapid fluctuation of gonadal hormones, such as premenstrually, postpartum, and during the climacteric. This review summarizes the evidence for the association of depression with abnormalities in reproductive hormones. Although there are similarities in stress hormones changes between depressed women and women with stress-related amenorrhea, no abnormalities in LH activity have been documented in depression. Similarly no abnormalities in LH, estradiol, or progesterone have been documented in premenstrual syndrome (PMS), although complete elimination of monthly cycling with leuprolide improves mood. Some studies have suggested beneficial effects of estrogen on mood in postmenopausal women but as yet there have been no adequately controlled studies of estrogen treatment of either premenopausal or postmenopausal women.

L129 ANSWER 18 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 1998101272 EMBASE
TITLE: Stabilisation of the hypothalamic-pituitary-adrenal axis as a treatment modality for mood disorders.
AUTHOR: Thakore J.H.
CORPORATE SOURCE: J.H. Thakore, Acad. Dept. of Psycholog. Medicine, Royal London Hospital, Alexadra Wing, London E1-1BB, France
SOURCE: Human Psychopharmacology, (1998) 13/2 (77-81).
Refs: 35
ISSN: 0885-6222 CODEN: HUPSEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 032 Psychiatry
037 Drug Literature Index
LANGUAGE: English

L129 ANSWER 19 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 93333805 EMBASE
DOCUMENT NUMBER: 1993333805
TITLE: The premenstrual syndrome: Theories of etiology with relevance to the therapeutic use of GnRH agonists.
AUTHOR: Shangold G.A.
CORPORATE SOURCE: R.W. Johnson Pharmaceut. Res. Inst., P.O. Box 300,Raritan, NJ 08869, United States
SOURCE: Seminars in Reproductive Endocrinology, (1993) 11/2

(172-186).
ISSN: 0734-8630 CODEN: SRENE8
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L129 ANSWER 20 OF 22 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2004-191046 [18] WPIDS
DOC. NO. CPI: C2004-075277
TITLE: New 1-amido-4-phenyl-4-benzyloxymethyl-piperidine derivatives useful as e.g. neurokinin-1 antagonists for treating e.g. **depression**, anxiety, cough and emesis.
DERWENT CLASS: B02 B03
INVENTOR(S): REICHARD, G A; SHIH, N; WANG, C; WANG, S; XIAO, D
PATENT ASSIGNEE(S): (SCHE) SCHERING CORP
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004004722	A1	20040115	(200418)*	EN	91

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CZ DE DK DM DZ EC EE ES FI GB GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LU LV MA MD MG MK MN MX MZ NI NO NZ PG PH PL PT RO RU SC SE SG SK SL SY TJ TM TN TR TT TZ UA UZ VC VN YU ZA ZM

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004004722	A1	WO 2003-US20783	20030702

PRIORITY APPLN. INFO: US 2002-393708P 20020703
ED 20040316
AB WO2004004722 A UPAB: 20040316
NOVELTY - 1-Amido-4-phenyl-4-benzyloxymethyl-piperidine derivatives (I) or their salts are new.
DETAILED DESCRIPTION - 1-Amido-4-phenyl-4-benzyloxymethyl-piperidine derivatives of formula (I) or their salts are new;
Ar1, Ar2 = (R19)n7-heteroaryl or phenyl (substituted by R8, R9 and R10);
X1 = e.g. -O-, -SO2, -NR12-, -N(COR12)- or -N(SO2R15);
R1, R3, R5, R25-R28 = H or 1-6C alkyl;
R2, R4, R6 = H, -CONR13R14 or -(CH2)n1-G;
G = e.g. H, -O-(1-6C)alkyl, SO2R13, -NR13R14, -SO2NR13R14, -NR13SO2R15, -NR13COR12, -NR12(CONR13R14), -CONR13R14, -COOR12 or 3-8C cycloalkyl;
CR1R2 = 3-6C cycloalkyl ring or -C(O)-;
CR3R4, CR5R6, CR23R24, CR25R26 and CR27R28 = -C(O)-;
R7, R11 = H, 1-6C alkyl, 3-8C cycloalkyl, (R16)n7-aryl-, (R19)n7-heteroaryl-, -COOR29, -CONR21R22, -CON(R21)(CH2)n-G1, -S(O)n5(CH2)n-G1, -S(O)n5R13, -CO(CH2)n-G1 or -(CH2)n1-G1;
n and n2+n3 = 0-4;
G1 = e.g. H, S(O)n5R13, -NR13R14, -NR13SO2R15, -CONR13R14, -COOR12,

(un)substituted (hetero)aryl;
NR7R11 = e.g. ring of formula (i);
X = e.g. -NR20-, -N(CONR13R14)-, -N(CO2R13)-, -N(SO2R15)-, -N(SO2NHR13)-;
R8-R10 = e.g. H, -COOR12, -NR21COR12, -NR21SO2R15, -S(O)n5R15, (un)substituted (hetero)aryl;
R12 = e.g. H, 3-8C cycloalkyl;
R13, R14 = e.g. H, (un)substituted (hetero)aryl;
NR13R14 = e.g. 4-7 membered ring;
R15 = e.g. 1-6C alkyl;
R16 = e.g. halo or -CF3;
R19 = e.g. -COOR12, -CONR21R22, -NR21R22, -NR21CO2R12, -NR21CONR21R22, -NR21SO2R15 or -S(O)n5R15;
R20 = e.g. H, 1-6C alkyl, (un)substituted (hetero)aryl;
R21, R22 = e.g. H, 1-6C alkyl;
NR21R22 = e.g. 4-7 membered heteroaryl ring;
R23, R24 = H, 1-6C alkyl, -CONR13R14;
R29 = e.g. 1-6C alkyl;
n1 = 1-4;
n2, n3, n6, n7 = 0-3; and
n4, n5 = 0-2.
Provided that:
(1) when X1 is -O- or NR12 then CR1R2 is -C(O)-;
(2) when n is 0, then G1 is H, 1-6C alkyl, alkenyl, -CON13R14, -COOR12, 3-8C cycloalkyl, CF3, (R16)n7-aryl-, -(R19)n7-heteroaryl or (R19)n7-heterocycloaryl;
(3) when n1 is 1 then G1 is H, 1-6C alkyl, alkenyl, -S(O)n5NR13, -SO2NR13R14, -CONR13R14, COOR12, 3-8C cycloalkyl, -CF3, (R16)n7-aryl-, (R19)n7-heteroaryl (where the heteroaryl ring is bound by a ring carbon to the -(CH2)n1 group) or (R19)n7-heterocycloalkyl (where the heterocycloalkyl ring is bound by a ring carbon to the -(CH2)n1 group); and
(4) when n4 is 0, R25 and R26 are H then X other than -O-, -NR20 or -S-.
Full Definitions are given in the DEFINITIONS Field (Full Definitions).
INDEPENDENT CLAIMS are also included for:
(1) composition (C) comprising (I) and carrier, and optionally at least one serotonin reuptake inhibitor;
(2) use of (I) in the manufacture of medicament for treating physiological disorder;
(3) treatment of physiological disorder involving administration of (I), in combination with at least one active ingredient selected from other neurokinin-1 (NK1) receptor antagonists, selective serotonin reuptake inhibitors, dopamine receptor agonists, serotonin 5-HT3 receptor antagonists, serotonin 5-HT2c receptor agonists, nociceptin receptor agonists, glucocorticoids and inhibitors of multidrug resistance protein 5 (preferably at least one serotonin 5-HT3 receptor antagonist (preferably ondansetron) and/or at least one glucocorticoid (preferably dexamethasone) or selective serotonin reuptake inhibitor);
(4) a kit comprising, in separate containers in a single package, a composition for use in combination to treat an NK-1 receptor mediated disease. One container comprises (C), and a separate container comprises composition comprising another therapeutic agent in carrier. The therapeutic agent is selected from SSRIs, other types of NK-1 receptor antagonists, prostanoids, H1 receptor antagonists, alpha -adrenergic receptor agonists, dopamine receptor agonists, melanocortin receptor agonists, endothelin receptor antagonists, endothelin converting enzyme inhibitors, angiotensin II receptor antagonists, angiotensin converting enzyme inhibitors, neutral metalloendopeptidase inhibitors, ETa antagonists, renin inhibitors, serotonin 5-HT3 receptor antagonists, serotonin 5-HT2c receptor agonists, nociceptin receptor agonists, glucocorticoids, rho kinase inhibitors, potassium channel modulators and

inhibitors of multi-drug resistance protein 5 (preferably SSRI); and

(5) a kit comprising, in separate containers in a single package, (C) for use in combination to treat depression and anxiety. One container comprises (C), and a separate container comprises a composition comprising an antidepressant agent in a carrier and/or where the separate container comprises a composition comprising an anti-anxiety agent in carrier.

ACTIVITY - Respiratory-Gen.; Antiinflammatory; Dermatological; Ophthalmological; CNS-Gen.; Anticonvulsant; Neuroleptic; Neuroprotective; Nootropic; Anti-HIV; Tranquilizer; Eating-Disorders-Gen.; Hypnotic; Antimanic; Gynecological; Gastrointestinal-Gen.; Antiarteriosclerotic; Anorectic; Antidiabetic; Analgesic; Antiemetic; Antidepressant; Antialcoholic; Anabolic; Antitussive; Antiemetic; Antiaddictive; Antiasthmatic; Antiallergic; Antiarthritic; Antipsoriatic.

MECHANISM OF ACTION - Neurokinin-1 (NK1) antagonist; Substance P at NK1 receptor site antagonist; NK1 receptor blocker.

The NK1 activity is measured by inhibition of agonist-induced foot tapping in gerbil as described in Science. 281, 1640-1695(1998). The compounds (I) show a Ki value of 11-0.3 nM.

USE - (I) Are used in medicaments for treating NK-1 receptor mediated disease and physiological disorder e.g. respiratory diseases, inflammatory diseases, skin disorders, ophthalmological disorders, central nervous system conditions, addictions, epilepsy, nociception, psychosis, schizophrenia, Alzheimer's disease, AIDS related dementia, Towne's disease, stress related disorders, obsessive/compulsive disorders, eating disorders, sleep disorders, mania, premenstrual syndrome, gastrointestinal disorders, atherosclerosis, fibrosing disorders, obesity, Type II diabetes, pain related disorders, bladder and genitourinary disorders, nausea, depression, anxiety, phobia, bipolar disorder, alcohol dependence, psychoactive substance abuse, stress related disorder, bulimia, anorexia nervosa, binge eating, headache, neuropathic pain, post-operative pain, chronic pain syndrome, cough and emesis (all claimed). Also for treating chronic lung disease, bronchitis, pneumonia, asthma, allergy, bronchospasm, arthritis, psoriasis, Crohn's disease, colitis, radiation-induced, motion sickness, ethanol-induced, post operative nausea, vomiting or psychoactive substance abuse.

ADVANTAGE - The compounds (I) are potent neurokinin-1 (NK-1) antagonists and possess beneficial therapeutic and pharmacological properties, and good metabolic stability.

Dwg.0/0

L129 ANSWER 21 OF 22 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-788200 [74] .WPIDS
DOC. NO. CPI: C2003-217620
TITLE: New substituted hetero(aryl)derivatives useful for treating e.g. respiratory disease, **depression**, anxiety, phobia, bipolar disorder.
DERWENT CLASS: B05
INVENTOR(S): REICHARD, G A; SHIH, N; WROBLESKI, M L; XIAO, D
PATENT ASSIGNEE(S): (SCHE) SCHERING CORP
COUNTRY COUNT: 99
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003078376	A1	20030925	(200374)*	EN	80

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CZ DE DK DM DZ EC EE ES FI GB GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LU LV MA MD MG MK MN MX MZ NI NO NZ PH PL PT RO RU SC SE SG SK SL TJ TM TN TR TT TZ UA UZ VC VN YU ZA ZM

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003078376 A1		WO 2003-US7633	20030312

PRIORITY APPLN. INFO: US 2002-363761P 20020313
ED 20031117
AB WO2003078376 A UPAB: 20031117
NOVELTY - Substituted hetero(aryl)derivatives, their salts and their solvates are new.
DETAILED DESCRIPTION - Substituted hetero(aryl)derivatives of formula (I), their salts and their solvates are new.
Ar1, Ar2 = heteroaryl (optionally substituted by (R21)r) or phenyl (trisubstituted by R10 - R12);
R1 - R3 = H, 1-6C alkyl, hydroxy(1-3C)alkyl, 3-8C cycloalkyl, -CH2F, -CHF2, or -CF3;
X1 = O, S, NR20, SO, SO2, N(COR20) or -N(SO2R17)-;
CR1+R2 = 3-6C cycloalkyl ring or -C(=O);
R4, R5, R8 and R9 = H, 1-6C alkyl, halo, -OR20, -O-C(O)NR15R16, -NR15R16, -NR15SO2R17, NR15C(O)R14, NR20C(O)NR15R16 or -SR20;
CR4+R5 = -C(=O)- or -C(=NR13)-;
R6 = -(CH2)n1-G;
n1, n6 = 0 - 5;
G = H, OH, O-1-6C alkyl, -O-(3-8C cycloalkyl), -O-C(O)NR15R16, -NR15R16, -NR15SO2R17, -NR15C(O)R14, -NR20C(O)NR15R16, -C(O)NR15R16, -C(O)OR20, 3-8C cycloalkyl or a group of formulae (ia) - (id);
X4 = O, S or -N(R20)-;
R7 = -(CR40R41)n6-J;
R40, R41 = H, methyl or ethyl;
J = H, CF3, CHF2, CH2F, OH, -O-(1-6C alkyl), -SO2R15, -O-(3-8C cycloalkyl), -O-C(O)NR15R16, -NR15R16, -SO2NR15R16, -NR15SO2R17, -NR15C(O)R14, -NR20C(O)NR15R16, -C(O)NR15R16, -C(O)OR20, 3-8C cycloalkyl or a group of formulae (ia) - (ie);
CR6+R7 = 4- - 7-membered heterocycloalkyl or heterocycloalkenyl ring (both comprising 1 - 4 heteroatoms of O, S, S(O), SO2, -N= or -NR20) or 4- - 7-membered carbon ring (all optionally mono- - tetra-substituted by R45), -(C=O)-, -C(=CH2)- or -C(=NR13)-;
R10 - R12 = T, H, -OR20, -CH2CF3, -OCH2CF3, -NR23CO2R17, -SO2NR23R24, aryl (optionally substituted by (R21)r), heteroaryl (optionally substituted by (R21)r);
R21 = OH, -O-(1-6C alkyl), -O-(3-8C cycloalkyl), -NR23CO2R20 or T;
T = 1-6C alkyl, 3-8C cycloalkyl, halo, -CN, -NO2, -CF3, -CHF2, -CH2F, -OCF3, -OCHF2, -OCH2F, -C(O)OR20, -C(O)NR23R24, -NR23C(O)R20, -NR23C(O)NR23R24, -NR23SO2R17, -NR23R24, or -S(O)n5R17;
R13 = OH or -O-1-6C alkyl;
R14 = H, 1-6C alkyl, 3-8C cycloalkyl, 1-6C alkyl-NH2 or 1-6C alkyl-NHC(O)O-1-6C alkyl;
R15, R16 = H, benzyl, 1-6C alkyl or 3-8C cycloalkyl; or
CR15+R16, CR23+R24 = 4- - 7-membered ring (optionally substituted by -OR20 and one of the carbon atoms is optionally replaced by -O-, -S- or -NR20);
R17 = 1-6C alkyl, 3-8C cycloalkyl or -CF3;
R20 = H, 1-6C alkyl, 3-8C cycloalkyl, -(1-6C)alkyl-NH2, (1-6C)alkoxy(2-6C) alkyl or hydroxy(2-6C alkyl);
R22 = H, 1-6C alkyl, 3-8C cycloalkyl or -(CH2)n4-heterocycloalkyl;
R23, R24 = H, 1-6C alkyl, 3-8C cycloalkyl or benzyl;
R25 - R28, R38, R39 = H or 1-6C alkyl; or
CR25+R26, CR27+R28 = -C(=O)- or cyclopropyl;
R29 = H, 1-6C alkyl or 3-8C cycloalkyl;
R30, R31 = H, 1-6C alkyl (preferably methyl or ethyl), -CH2F, -CHF2, -CF3, -OH or -O-(1-3C)alkyl;
CR30+R31 = -C(=O)- group;

CR38+R39 = cyclopropyl group;
R45 = 1-6C alkyl (preferably methyl or ethyl), -CH2F, -CHF2, -CF3, -OH or -O-(1-3C)alkyl; or
CR45+R45 = -C(=O)- group;
X2 = -CH2-, -NR22-, -N(C(O)NR15R16)-, -N(CO2R15)-, -N(SO2R17)-, -N(C(O)R20)-, -N(SO2NHR20), -O-, -S-, -S(O)-, -SO2- -CF2- or -CR20F-;
r = 1 - 3;
n2 = 1 - 4;
n3, n5 = 0 - 2;
n4, n9 = 0 - 3; and
n8 = 0 - 4;
Provided that:
(a) when n1 is 0, then G is OH, O-1-6C alkyl, -O-(3-8C cycloalkyl), -O-C(O)NR15R16, -NR15R16, -NR15SO2R17, -NR15C(O)R14, -NR20C(O)NR15R16 or a group of formulae (ia) - (id);
(b) when n6 is 0, then J is H, CF3, CHF2, CH2F, C(O)NR15R16, C(O)OR20 or (ie);
(c) when n1 and n6 are 0, then one of the R6 and R7 is bound through a heteroatom to the ring carbon of cyclobutane ring, then the other of R6 and R7 is bound through a carbon atom to the ring carbon of the cyclobutane ring;
(d) for CR6+R7, a ring -S- in the heterocycloalkyl or heterocycloalkenyl rings is not bound to another ring S- or ring -S(O) or ring -O- and a ring -O- in the heterocycloalkyl or heterocycloalkenyl rings is not bound to another ring -O-;
(e) when n3 is 0, R27 and R28 are H, then X2 is -CH2, -S(O)-, SO2, -CF2 or -CR20F-;
(f) when X1 is SO, SO2, N(COR20) or -N(SO2R17)- then CR1+R2 is 3-6C cycloalkyl ring; and
(g) when X1 is O, S or NR20, then CR1+R2 is 3-6C cycloalkyl ring or -C(=O);
INDEPENDENT CLAIMS are included for the following:
(1) a pharmaceutical composition comprising (I), a carrier and an optional at least one serotonin reuptake inhibitor; and
(2) use of (I) in the manufacture of a medicament for the treatment of physiological disorder e.g. respiratory disease, emesis.
ACTIVITY - Respiratory-Gen.; Antiinflammatory; Antiasthmatic; Antiallergic; Antitussive; Antiarthritic; Antipsoriatic; Dermatological; Ophthalmological; Hypotensive; CNS-Gen.; Antidepressant; Neuroleptic; Antiaddictive; Antialcoholic; Anticonvulsant; Nootropic; Neuroprotective; Anti-HIV; Tranquilizer; Eating-Disorder-Gen.; Anabolic; Hypnotic; Antimanic; Gynecological; Gastrointestinal-Gen.; Antiemetic; Antiarteriosclerotic; Anorectic; Antidiabetic; Analgesic; Antimigraine; Uropathic; Cytostati.
MECHANISM OF ACTION - Neurokinin-1 (NK1) receptor antagonist; Antagonist of an effect of a Substance P at a NK-1 receptor site; NK-1 receptor blocker.
The in vitro NK1 activity of 3-(1-(3,5-bis-trifluoromethyl-phenyl)-ethoxymethyl)-2,2-dichloro-3-phenyl-cyclobutanone (Ia) was determined as given in Duffy, Rutg A. et al.,Correlation of Neurokinin (NK)1 Receptor Occupancy in Gerbil striatum with Behavioural Effects of NK1 Antagonists, J Pharmacol Exp Ther, 2002, 301:536 - 542. and (A) showed an inhibition constant (Ki) of 0.02 - 93.20 nM.
USE - In the manufacture of a medicament for the treatment of physiological disorder e.g. respiratory disease, depression, anxiety, phobia, bipolar disorder, alcohol dependence, psychoactive substance abuse, nociception, psychosis, schizophrenia, stress related disorder, obsessive/compulsive disorder, bulimia, anorexia nervosa, binge eating, sleep disorder, mania, premenstrual syndrome, gastrointestinal disorder, obesity, headache, neuropathic pain, post-operative pain, chronic pain syndrome, bladder disorder, genitourinary disorder, cough, nausea or emesis and for antagonizing an effect of a Substance P at a neurokinin-1 receptor site or for blocking at least one NK-1 receptor (claimed).

ADVANTAGE - The compounds are potent and selective NK1 antagonist and minimize side effects.
Dwg.0/0

L129 ANSWER 22 OF 22 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1995-051951 [07] WPIDS
DOC. NO. CPI: C1995-023792
TITLE: analogues of known drugs, many CNS active - also used in cancer, heart arrhythmias, and in surgery.
DERWENT CLASS: B05
INVENTOR(S): BARF, T A; WIKSTROM, H; WIKSTROEM, H
PATENT ASSIGNEE(S): (LUND) LUNDBECK AS H
COUNTRY COUNT: 46
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9500478	A1	19950105	(199507)*	EN	42
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: AT AU BB BG BR BY CA CH CN CZ DE DK ES FI GB HU JP KP KR KZ LK LU LV MG MN MW NL NO NZ PL PT RO RU SD SE SK UA US UZ VN					
AU 9469955	A	19950117	(199521)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9500478	A1	WO 1994-DK244	19940620
AU 9469955	A	AU 1994-69955	19940620

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9469955	A	Based on	WO 9500478

PRIORITY APPLN. INFO: DK 1993-726 19930618
ED 19950223
AB WO 9500478 A UPAB: 19950602
The subject matter covers aryltriflate analogues of known drugs. Triflate (and some other sulphonyl) analogues of raclopride (of formulae A1 and A2), riluzole (of formula B), cisapride (of formulae C1 and C2), omeprazole, lanzoprazole, or pantoprazole (of formula D), paroxetine (of formula E), fenfluramine (of formula F), sotalol (of formula G1 and G2), 3alpha- and 3beta- oestradiol triflates, **RU 486** (of formula H), tacrine (of formula J), moclobemide (of formula K), ifenprodil (of formula L), brofaromine (of formulae M1 or M2), melatonin (of formula N), N-acetyl-2-[(7-triflyloxy-1-naphthyl)ethyl]amine, prenalterol (of formula P), sumatriptane (of formula Q, 2-amino-6-triflyloxy-1,2,3,4-tetrahydrocarbazole, mianserin (of formula S), aza-hydrophenantrenes (of formula T), or carbamazepine (of formula U), and their salts are new. Tf = triflyl (CF3SO2O); in B; RB = CF3, 1-8C alkyl, 3-8C cycloalkylmethyl, or phenyl or phenyl 1-8C alkyl (both opt. substd. by halo or 1-4C alkyl), thienyl, or thienyl 1-8C alkyl; in D; (A,B,C,D) = (Me, OMe, Me, Tf)(omeprazole), (H, Tf, Me, H) (lanzoprazole), or (H, OMe, OMe, Tf) (pantoprazole);p in J; RJ = as RB in B; in L; RL = as RB in B; in Q, R1,R2 = H, 1-8C alkyl or haloalkyl, 2-8C alkenyl or alkynyl, cycloalkyl, cycloalkyl 1-8C alkyl, phenyl 1-8C alkyl, or heteroaryl 1-8C alkyl; and RQ = CF3, 1-8C alkyl or haloalkyl, or phenyl or phenyl 1-8C alkyl (both opt. substd. by halo or 1-4C alkyl); in S; RS =CF3, 1-8C alkyl, 3-8C cycloalkylmethyl, or phenyl or phenyl 1-8C alkyl (both opt. substd. by halo or 1-4C alkyl), thienyl or thienyl or 1-8C alkyl, and R3 = 1-4C alkyl.

USE - Uses are as for the parent drugs. A1 and A2 are D2 and D3 antagonists, useful in treatment of psychoses, partic. schizophrenia. B are NMDA antagonists useful in prevention or treatment of neurodegeneration ALS, MS, stroke, Alzheimer's disease, ageing, heart infarction, or in traffic accident victims, open heart surgery, and post-operative treatment. C1 and C2 are 5-HT4 antagonists, useful in prevention of irritable bowel syndrome, and promoting stomach emptying and intestinal motility, partic. the colon. D are K+ and H+ ATPase inhibitors useful in treatment or ulcer, reflux oesophagitis, and Zollinger-Ellison syndrome. E are selective **5-HT reuptake inhibitors**, useful in panic disorders, anxiety and **depression**. F also acts on 5-HT receptors, in the brain, and use is prevention of autism. G1 and G2 are class III anti-arrhythmic agents for treatment of heart arrhythmias. The oestradiol esters are used in treatment of breast and ovarian cancer. **RU 486** has reproductive system effects, used in early foetal abortion.

ADVANTAGE - The cpds. have high oral potency and long duration of action, compared to hydroxy or alkoxy analogues. The triflyl tacrine has better pharmacokinetic properties then tacrine itself; and the riluzole analogue is less toxic.

Dwg.0/0

FILE 'HOME' ENTERED AT 10:27:25 ON 21 APR 2004